

**CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT  
FOR THE SLEEP APNOEA/HYPOPNOEA SYNDROME**

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## ABSTRACT

The preferred form of treatment for the sleep apnoea/hypopnoea syndrome (SAHS) is continuous positive airway pressure (CPAP). This thesis investigates the usage, benefits to patients and partners, and method of initiation of CPAP therapy.

A database of all 1,211 patients booked for CPAP between 1986-1997 was constructed, with 95.4% follow-up at a median of 22 months. Fifty-two (4.5%) patients refused CPAP treatment; these were more often female and current smokers. The methods of survival analysis found 68% of patients continued treatment at 5 years and the independent baseline predictors of continued CPAP use were snoring history, apnoea/hypopnoea index (AHI), and Epworth sleepiness score (ESS). CPAP use at 3 years was  $\geq 92\%$  in sleepy patients with severe disease ( $ESS > 10$ ,  $AHI > 60$ ) but only 40% in non-sleepy mild severity patients ( $ESS \leq 10$ ,  $AHI < 15$ ). Average nightly use within 3 months was strongly predictive of long-term use.

Using the above database the independent predictors of long-term use were used to match ( $AHI \pm 15\%$ ,  $ESS \pm 3$ ) 46 patients prescribed split-night (diagnostic + CPAP titration studies in 1 night) studies with 92 full night patients. Classical symptoms of SAHS were the main reason for split-night studies ( $n=27$ ). There was no difference between these split and full night studies in long-term CPAP use, median (IQR) nightly CPAP use [split 6.0 (3.8-7.4)hr/night, full 6.2 (3.7-7.0)hr/night,  $p=0.9$ ], post-treatment ESS, or frequency of nursing

interventions/clinic visits required. Split-night patients received treatment quicker [median (IQR) time from referral to treatment 13 (11-20) versus 22 (12-34) months,  $p=0.003$ ].

In a randomised crossover study 22 unselected SAHS patients [median (IQR) AHI = 40(25-65)] events/hr had 1 month limbs on CPAP and placebo capsules, and home polysomnography was performed at the end of each month. During CPAP patients had a lower arousal index, less stage 1 and more stage 3+4 sleep (all;  $p\leq 0.03$ ), but no increase in stage REM sleep. In the above study the partners' sleep quality was also monitored while the patient received CPAP and placebo. There was no difference in the partners' objective sleep quality between CPAP and placebo. However partners reported improved subjective sleep quality ( $p=0.05$ ) and less disturbance to sleep ( $p=0.03$ ) during the patients' use of CPAP compared to placebo.

Thus long-term CPAP use is related to disease severity and subjective sleepiness and can be predicted within 3 months. Low usage in mild patients with few symptoms suggests alternative treatments are needed. These studies also show that treatment waiting time and cost can be reduced, with no loss of effectiveness, by performing split-night studies in selected patients. Patients with SAHS have better objective sleep quality and their partners have improved subjective sleep quality when the patient is treated with CPAP.

## **DECLARATION**

I declare that I was the principal investigator in all of the studies conducted within this thesis and that the contents of this thesis are my own work. Assistance with these studies was provided by other staff members of the Edinburgh sleep centre, as outlined in the acknowledgements.

The studies reported in this thesis were conducted between May 1997 and the December 1999. They were conducted in the Edinburgh sleep centre or, as home studies, within Scotland.

Dr Nigel McArdle

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## **ABBREVIATIONS**

AHI – Apnoea/hypopnoea index

BMI – Body mass index

CI – Confidence interval (e.g., 95% CI)

COPD – Chronic obstructive pulmonary disease

CPAP – Continuous positive airway pressure

CT – Computerised tomography

CVS – Cardiovascular system

EDS – Excessive daytime somnolence

EEG - Electroencephalography

EMG - Electromyography

EOG - Electroculography

ESS – Epworth sleepiness score

FOSQ – Functional outcomes of sleepiness questionnaire

hr(s) – Hour(s)

IQR – Interquartile range

min – Minutes

MmHg – millimeters of mercury

MMO - Maxillomandibular advancement osteotomy

MRI – Magnetic resonance imaging

MRS – Mandibular repositioning splint

NREM – Non-rapid eye movement sleep

OHS – Obesity hypoventilation syndrome

PSG – Polysomnography

REM – Rapid eye movement sleep

RDI – Respiratory disturbance index

SAHS – Sleep apnoea/hypopnoea syndrome

sd – Standard deviation

SDB – Sleep disordered breathing

SEI – Sleep efficiency index

SF 36 – Short form 36 quality of life questionnaire

(SHHS) - Sleep Heart Health Study

SURT – Simple unprepared reaction time

TRT – Total recording time

TST – Total sleep time

UPPP – Uvulopalatopharyngoplasty

yr(s) – Year(s)

## **CHAPTER 1 – THE SLEEP APNOEA/HYPOPNOEA SYNDROME: OVERVIEW**

## **1.1 History and introduction:**

As far back as the early nineteenth century medical writers recognised the association between obesity and hypersomnolence (Wadd 1810). Recognition of this association was popularized by Charles Dickens' (Dickens 1837) classic description of the fat boy 'Joe' in the *'The posthumous papers of the Pickwick club'*. It was not until the latter half of the twentieth century that the importance of pathophysiological changes during sleep (Gastaut et al. 1966) were identified as contributing to a range of abnormalities which were then called the Pickwickian syndrome. The main features of the Pickwickian syndrome were marked obesity, hypersomnolence, cyanosis, polycythemia, and right sided heart failure (Burwell et al. 1956). Subsequently, it became clear that there were two disorders, which can act together or separately, to produce features of the Pickwickian syndrome (Guilleminault et al. 1976, Sullivan et al. 1983). One of these was the obesity/hypoventilation syndrome (OHS) whereby obesity is associated with hypoventilation not only during sleep but also during the awake state. In this condition there is daytime hypercapnia and hypoxia. The other disorder was obstructive sleep apnoea or, as it is more accurately known, the sleep apnoea/hypopnoea syndrome (SAHS). The SAHS occurs not only in obese individuals but also in the non-obese, and is associated with periodic hypoventilation during sleep without detectable respiratory abnormalities in the awake state (Guilleminault et al. 1976).

Early investigators often diagnosed patients with severe SAHS who had associated cardiovascular compromise (some may have also had OHS). Treatment with tracheostomy, introduced in Europe in the late 1960's, produced dramatic improvements in symptoms as well as in cardiovascular dysfunction (Coccagna et al. 1972). Improvement by tracheostomy provided strong evidence that the primary abnormality in SAHS was (intermittent) obstruction occurring in the collapsible part of the upper airway, i.e., above the glottis. Further work showed that collapse of the upper airway was a passive phenomenon secondary to negative transmural pressure and that during episodes of airway collapse there was relative hypotonia of upper airway muscles in relation to negative inspiratory pressure in the upper airway (Guilleminault et al. 1978a, Remmers et al. 1978). At the end of an episode of airway collapse airway patency was re-established immediately after electroencephalographic (EEG) 'arousal' with preferential activation of the upper airway muscles (Remmers et al. 1978).

In 1981 Colin Sullivan and colleagues tested the hypothesis that the passive collapse of the upper airway during sleep in patients with SAHS could be abolished by the application of a relatively low ( $<20$  cm H<sub>2</sub>O) but continuous, positive airway pressure (CPAP) through the nares (Sullivan et al. 1981). This treatment was highly successful in providing rapid relief of symptoms and has since become the preferred form of treatment for most patients with SAHS [Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnea syndromes. American Thoracic Society, 1994]. Further, the ability to treat SAHS patients successfully in a



non-invasive, if somewhat inconvenient, way stimulated further interest in the SAHS. This thesis investigates the use of CPAP to treat the SAHS.

## **1.2. Definition of the SAHS and sleep disordered breathing:**

### ***1.2.1 Sleep apnoea/hypopopnoea syndrome***

The SAHS occurs because the upper airway collapses intermittently during sleep. Collapse of the upper airway can be complete with total obstruction to the airway lumen and no respiratory airflow or partial with reduction in the size of the upper airway lumen causing hypoventilation. Episodes of complete cessation of respiratory airflow are called apnoeas and were the main abnormalities recognised in early studies of this condition (Guilleminault et al. 1978b). It was subsequently discovered that episodic hypoventilation, i.e., hypopnoeas, could also cause the symptoms attributed to repeated apnoeas (Gould et al. 1988). Hypopnoeas are recognised by varying criteria in different sleep centres but most definitions require some reduction in chest and abdominal wall movement or reduced airflow. In some centres hypopnoeas are defined using additional criteria including an associated oxygen 'dip' (desaturation) or an EEG arousal. The frequency of apnoeas and hypopnoeas per hour of sleep is an important measure that is widely used to assess the severity of the SAHS and is called the apnoea/hypopnoea index (AHI). In some centres this index is called the respiratory disturbance index (RDI). As these indices are defined in different ways in different centres comparisons between centres can be difficult. Recommendations aiming to

standardise definitions of apnoeas and hypopnoeas and related indices have recently been published (Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. 1999). The sleep apnoea/hypopnoea syndrome is the combination of frequent apnoeas/hypopnoeas during sleep (the diagnostic threshold varies between sleep centres) and the presence of typical clinical features. The clinical manifestations of this syndrome, the most important being daytime hypersomnolence, are described in more detail below (chapter 1.5.1).

### ***1.2.2 Upper airways resistance syndrome and sleep disordered breathing***

In 1993 Guilleminault and colleagues described a new cause of daytime somnolence called upper airways resistance syndrome (UARS). This syndrome was thought to occur due episodes of increased respiratory effort (assessed using oesophageal monitoring) without clearly identifiable apnoeas or hypopnoeas (Guilleminault et al. 1993). Episodic increases in upper airway resistance were associated with transient EEG arousals which, along with daytime sleepiness, were abolished with CPAP treatment. There remains some dispute about the existence of this syndrome as a distinct entity (Douglas 2000). In the studies by Guilleminault and colleagues increases in inspiratory effort were associated with airflow limitation, recognised by flattening of the inspiratory flow contour. It is postulated that flattening of the flow contour may be

used to identify milder forms of breathing irregularity, than apnoeas and hypopnoeas, which may also cause sleep disturbance (Condos et al. 1994).

Snoring, by itself, does not appear to be associated with cardiovascular disease (Hoffstein 1996) and it is unknown if there is an association with impaired daytime dysfunction (Hoffstein et al. 1995). But snoring (when other sleep disorders are excluded, apart from UARS) seems to be weakly associated with an increased frequency of EEG arousals (Hoffstein et al. 1995). There is evidence from repeated PSG studies suggesting that disease progresses over time from snoring alone through to increasing severity of SAHS (Svanborg & Larsson 1993, Lindberg et al. 1999). This lends support to the concept, first proposed by Lugaresi and colleagues (Lugaresi et al. 1983), that there is a continuum of disease, from simple snoring to UARS to increasingly severe SAHS. Together these conditions are thought to form part of a spectrum of disorders with breathing abnormalities during sleep, often referred to as sleep-disordered breathing (SDB). In this thesis, although reference will be made to the spectrum of diseases associated with SDB, only the well-characterized condition of SAHS will be discussed in detail.

### **1.3. Epidemiology:**

SDB is very prevalent in the community. One large community study found 24% of men and 9% of women had an  $AHI \geq 5/hr$  and, using more stringent criteria for abnormality, 9% of men and 4% of women had an  $AHI \geq 15/hr$  (Young et al. 1993). The

SAHS (i.e., typical symptoms and increased AHI) is also prevalent, with an estimated 2-4% of the middle-aged population meeting the minimum criteria for this diagnosis (Young et al. 1993). There are 3 common epidemiological associations with SDB and SAHS: male sex, increasing age, and increasing obesity. Studies of a number of different population groups have shown that SAHS is more common in men, but the ratio of men to women is higher in clinic-based surveys (approximately; men:women = 8:1) (Guilleminault et al. 1988) than in community-based ones (approximately; men:women = 2:1) (Young et al. 1993). This is thought to be due to differences in the type or severity of symptoms experienced by men and women (perhaps because of a blunter arousal response in the former) for the same frequency of respiratory events and/or due to referral bias. Studies have usually shown that SAHS increases with age between approximately 30 and 65 years (Stradling & Crosby 1991), although some have not (Young et al. 1993). SDB is very common in the elderly (age >65 years) (Ancoli-Israel et al. 1985), but some of this increase may be due to increased numbers of central apnoeas (secondary to age, cardiac, and cerebrovascular disease or even to poor sleep quality) and is usually not associated with sleep-wake complaints (80% report satisfactory sleep) (Ancoli-Israel et al. 1985). Most epidemiological studies investigating anthropometric variables have shown a strong and independent association of SAHS with measures of obesity, particularly measures of central obesity (i.e., neck circumference and hip:waist ratio) (Young et al. 1993, Stradling & Crosby 1991).

## **1.4. Physiology:**

### ***1.4.1 Forces acting on the upper airway***

The upper airway is not held open by rigid support and a number of forces acting in opposing directions determine the patency of the upper airway. The static forces acting on the upper airway include surface adhesive forces and gravitational forces, especially in the supine or lateral recumbent position, which both tend to close the airway. Superimposed on these passive forces are dynamic changes occurring during respiration. Of particular importance are the changes during inspiration, when negative pressure is generated in the airways in order for air to flow from through the nose/mouth to the lungs. In addition, for a given pressure difference the rate of flow and inward forces increase as a tube narrows, known as the Bernoulli effect. Hence, anatomical narrowing and static and dynamic forces interact to produce negative pressures in the pharynx and a tendency to airway collapse.

The maintenance of a patent upper airway is in large part due to the action of the pharyngeal dilator muscles, which act both tonically and phasically (i.e., synchronous with inspiration) to increase the pharyngeal area and reduce upper airway compliance. Tissue elastic components also act to help maintain a patent airway (Sullivan et al. 1981).

#### *1.4.2 The upper airway of normal subjects compared with SAHS patients*

Patients with SAHS appear to have both anatomical and physiological pharyngeal abnormalities that predispose to airway collapse. For example, the pharyngeal cross-sectional area, when measured using acoustic reflection techniques, is smaller than in normal subjects (Bradley et al. 1986). Further, using the same techniques, there are lung-volume dependent changes in pharyngeal cross-sectional area (reductions as lung volumes decrease) that do not occur in patients with simple snoring (Bradley et al. 1986), suggesting SAHS patients have a more compliant pharyngeal airway wall. Not all investigators have found that patients with SAHS have small upper airways. There appears to be, at least partial, compensation during wake by increased activity of pharyngeal dilator muscles, such as genioglossus, as measured as a percentage of maximal activity (Mezzanotte et al. 1992) – possibly explaining such anomalous findings. This compensation is thought to be mediated through local reflex responses to increased negative intraluminal pharyngeal pressure (Mezzanotte et al. 1992).

Resistance to airflow in the nasopharynx correlates with the AHI among patients with SAHS (Suratt et al. 1985). Patients with nasal congestion or narrowing for anatomical or pathological reasons will tend to have more negative pressures in the upper airway. In addition to nasopharyngeal abnormalities, other clinically recognisable anatomical abnormalities are known to predispose to SAHS, including micrognathia, retrognathia (as in the Pierre-Robin syndrome), macroglossia (for example due to acromegaly), and tonsillar hypertrophy. However, most patients with SAHS have no such clinical



disorder but have more subtle anatomical abnormalities that can be detected using cephalometric or other imaging techniques (Rivlin et al. 1984).

The association of SAHS with obesity is probably in part due to increased fat deposits lateral to the pharynx (in a space between the pterygoid muscles and the carotid artery) as well as in the soft-palate and uvula. Shelton and colleagues (Shelton et al. 1993) found that in SAHS the AHI correlated well with the volume of fat in this space as measured using magnetic resonance imaging (MRI) ( $r = 0.59$ ,  $p < 0.001$ ). This suggests a pathogenic role of pharyngeal fat deposits, perhaps by increased loading on the lateral pharyngeal walls.

#### ***1.4.3 Upper airway during sleep in normal subjects***

During sleep in normal subjects there is reduction in the basal activity and response to resistive loading of tonic pharyngeal muscles, such as tensor palatini, with little change in the activity of phasic muscles such as genioglossus (Tangel et al. 1992). There is also a loss of reflex activation of the genioglossus muscle, as assessed by brief negative-pressure waves (Wheatley et al. 1993). This leads to a shift in the balance of forces operating on the upper airway so that there is a more negative pressure in the pharynx. Hence, even in normal subjects there is some airway narrowing and an increase in upper airway resistance (White 1995).

#### ***1.4.4 Upper airway during sleep in the SAHS***

It is thought that during sleep there is a loss of the compensatory mechanisms necessary to maintain upper airway patency in awake SAHS patients (Wheatley et al. 1993), mainly reflex phasic dilator muscle activation (Mezzanotte et al. 1992). Hence during sleep the stronger inward forces in the airway of these patients overwhelm outward forces, leading to recurrent apnoeas and/or hypopnoeas. From the above description of the forces operating on the upper airway in the awake and asleep state it is evident that both anatomical and/or neuromuscular factors can predispose to apnoeas and hypopnoeas. It is currently unclear which of these mechanisms is most important. Furthermore, the site of obstruction varies between individuals and usually there are a number of different sites of significant narrowing in the same person (Morrison et al. 1993). Although the nasopharyngeal (retropalatal) site is commonly involved, it is infrequently the only site of obstruction (Morrison et al. 1993).

#### ***1.4.5 The arousal response***

Termination of apnoeas and hypopnoeas is usually associated with immediately preceding EEG changes of increased cortical activity (Remmers et al. 1978). The increased cortical activity is called an arousal and is thought to lead to increased pharyngeal dilator muscle activity, terminating the obstructive episode (Remmers et al. 1978). Arousals also occur without changes seen on the EEG, which can be detected by changes in vascular reactivity (autonomic response), probably operating at a brainstem



level (Davies et al. 1993). Arousals may lead to a change in sleep state, for example to a sustained period of wakefulness, but in the SAHS arousals are usually brief (in the order of seconds or less) (Stepanski et al. 1984) and not associated with conscious recollection. Arousals are clearly important because of their central role in terminating obstructive respiratory events.

#### ***1.4.6 Sleep architecture in SAHS***

Sleep is divided into two main types: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is classified further into four stages (1-4) which parallel the sleep depth (as indicated by difficulty rousing the sleeper) (see chapter 3.4 for further detail). Poor quality sleep has been found among SAHS patients in studies comparing SAHS patients to normal subjects (Bedard et al. 1991, Stepanski et al. 1984). In these studies SAHS patients have less 'deep' sleep (stage 3+4) and more 'light' sleep (stage 1), and in one of the studies (Bedard et al. 1991) less REM sleep in a group of severe SAHS patients.

#### ***1.4.7 Aetiology of symptoms in SAHS***

Brief arousals produced by tones in normal subjects result in daytime sleepiness and impaired cognitive function (Martin et al. 1996). It is thought that arousals are important in causing many of the daytime symptoms of SAHS. Patients with SAHS

usually have more than 40 (if sleeping for 8 hrs) to, in some patients, many hundreds of respiratory-related arousals during the night.

However, the relationship of arousals, as currently assessed, to important symptoms (such as daytime sleepiness) in SAHS patients is weak and of little clinical use. In a large prospective correlational study by Kingshott and colleagues (Kingshott et al. 1998) only weak relationships were found between standard nocturnal PSG variables and measures of daytime function among patients with SAHS. Nocturnal variables studied included arousal frequency, AHI, and oxygen desaturation indices. By contrast, in a sample which was not restricted to patients with SAHS (some non-snorers were included), arousal indices were stronger predictors of daytime sleepiness and of improvement in sleepiness with CPAP treatment (Bennett et al. 1998).

The reason that standard nocturnal PSG variables are weakly associated with important daytime symptoms, such as hypersomnolence and cognitive dysfunction, in SAHS may be because they do not measure the important pathophysiological changes (e.g., 'autonomic arousals' may be better or a more direct measure of sleep consolidation may be better). Further, there are other potential factors contributing to symptoms (e.g., poor sleeping habits) and difficulties in assessing daytime dysfunction (e.g., objective sleepiness tests are also influenced by motivation). There may also be factors related to the time course of the illness, i.e., individual rates of habituation to arousals over time, that are not modeled in experimental studies on normal subjects (Chugh et al. 1996).

Arousals are thought to lead to daytime SAHS symptoms by disrupting or fragmenting the normal sleep structure leading to poor quality sleep. Some authors (Chugh et al. 1996, Stepanski et al. 1984) found significant, albeit relatively weak, associations between daytime sleepiness in SAHS and objective measures of sleep quality simultaneously with arousal frequency. There are interrelationships between many of the standard nocturnal variables measured (e.g., AHI and arousal index), but there is little work on the relationship of sleep architecture variables and daytime sleepiness and response to CPAP treatment.

#### ***1.4.8 Cardiovascular consequences of SDB***

One of the earliest physiological observations among patients with SAHS was the presence of cyclical changes, which were often marked, in blood pressure and heart rate coinciding with apnoeas/hypopnoeas. There are similar cyclical changes in pulmonary artery pressure. Rises in blood pressure occur at the end of apnoeas/hypopnoeas and seem to be largely caused by the arousal per se (as part of an 'orienting reflex') rather than other physiological stimuli, such as hypoxia occurring with each apnoea/hypopnoea (Davies et al. 1993). Further, blood pressure does not just oscillate about an unchanged mean value during the night but is elevated overall during sleep where there are apnoeic periods, whereas in normal subjects it falls compared to daytime blood pressure (Davies et al. 1994). There are also elevations of urinary catecholamines among patients with SAHS compared to controls (Marrone et al. 1993). Levels of adrenaline in SAHS appear to be most relevant because the elevated levels of

adrenaline are found at night as well as during the day and are reduced by CPAP treatment; nor-adrenaline levels fall at night and are not influenced by CPAP (Marrone et al. 1993).

It is unknown if these acute cardiovascular changes lead to the development of cardiovascular disease, but current evidence for a causative link between SDB and cardiovascular diseases will be discussed (chapter 1.7.2).

## **1.5. Diagnosis of SAHS:**

### ***1.5.1 Clinical features***

Early investigators (Whyte et al. 1989, Sullivan & Issa 1985, Guilleminault et al. 1978b) described a range of symptoms as part of the SAHS. These included (in approximate order of frequency): loud snoring, excessive daytime sleepiness, witnessed apnoeas or choking during sleep, decreased libido/impotence, nocturia, restless sleep, and morning headache. It was observed that there can be intellectual deterioration and personality change. Other less common symptoms are also sometimes found, such as ankle oedema when SAHS is complicated by cor-pulmonale (Sullivan & Issa 1985) or even hypnagogic hallucinations as a non-specific consequence of severe sleepiness (Guilleminault 1989).

Some of these symptoms, such as history of snoring and apnoeas, are best obtained from the bed partner. Data from a community epidemiological study (Stradling & Crosby 1991) found a higher prevalence of reported “snoring often” when the wife is present at interview compared with not present (23% versus 10%,  $p < 0.0001$ ). This suggests that patients may underestimate or be less aware of their nocturnal symptoms than their partner. Another study found more missing questionnaire data about SAHS symptoms in unmarried subjects compared to married subjects suggesting that subjects themselves may be poorly aware of some of these symptoms (Kump et al. 1994).

Examination provides little direct evidence of SAHS, apart from suggestive features such as decreased alertness in the clinic, obesity (especially ‘central’, including a thick neck), obvious retrognathia, or naso-pharyngeal narrowing (Douglas 1988). Even brief observation of patients while they sleep by a clinician, although of high specificity, is not an effective screening procedure for detecting SAHS (Haponik et al. 1984). Examination is useful to look for underlying causes of SAHS (although SAHS is not usually secondary to another disease), such as hypothyroidism or acromegaly, and for complications of SAHS in other organ systems, such as the presence of hypertension or right heart failure (Douglas 1988).

The subjective impression that a clinician gains from patient and partner symptoms is not very accurate at predicting the presence of SAHS, with a diagnostic accuracy of 63% (Viner et al. 1991). This may be because the symptoms of SAHS are either common (e.g., snoring) or have many other causes and so by themselves are not very

specific (e.g., daytime sleepiness). Further, the use of predictive equations based on a range of symptoms and basic anthropometric data are not sufficiently accurate to make a diagnosis in the clinic (Viner et al. 1991). A recent study found the use of neural networks (instead of analysis by multiple regression) may be more accurate and in this study the predictive accuracy of information from history and examination was over 80% for commonly used RDI diagnostic thresholds (el Solh et al. 1999).

### ***1.5.2 Investigation***

As clinical assessment alone is unable to adequately differentiate patients that have SDB from those that don't, an investigation assessing a range of physiologic changes during sleep, i.e., a sleep study, is needed to diagnose this condition (Chesson et al. 1997). The gold standard investigation is full polysomnography (PSG) in which the following signals are usually recorded: electroencephalography (EEG); electroculography (EOG); sub-mental electromyography (EMG); airflow (nose and mouth); thoracic and abdominal movement; oxygen saturation by oximetry; snoring sounds and body position. Full PSG is recommended for most patients but it is also acceptable to perform other 'limited' sleep studies providing there is a high pre-test probability of disease and full PSG is performed if the limited study is negative (Practice parameters for the indications for polysomnography and related procedures. Polysomnography Task Force, American Sleep Disorders Association Standards of Practice Committee 1997). Limited studies range from simple oximetry alone to recordings of cardiorespiratory signals (such as airflow, chest and abdominal



movement, electrocardiography, and oxygen saturation) without EEG. Another alternative that is sometimes used in many centers has been to combine diagnosis and (CPAP) treatment into a single night, called a split-night study. During split-night studies an assessment is made in the first half of the night about the presence of SDB, if there is clear evidence of SDB above a pre-determined threshold CPAP treatment is established in the remainder of the night. In this thesis we describe the first controlled assessment of long-term outcomes of split-night studies.

## **1.6 Public Health consequences of SAHS:**

### ***1.6.1 SAHS and effects on daytime function***

The SAHS is prevalent in the community. Further, the consequences of the SAHS on daily function are widespread and include sleepiness, impairments in cognitive function, mood, and personality (Engleman et al. 1994a). Not surprisingly, SAHS is associated with reduced quality of life, with one study showing reductions in all dimensions measured in a standard quality of life questionnaire (Smith & Shneerson 1995). Further, there can be adverse effects on others, including impaired relationships between spouses and partners (Cartwright & Knight 1987).

The symptoms of sleepiness and impaired concentration from SAHS are thought to have serious consequences during activities where reduced alertness is dangerous. Teran-Santos and colleagues (Teran-Santos et al. 1999) found that drivers with an AHI

>10 had an increased odds ratio of 6.3 [95% confidence interval (CI) = 2.4-16.2] of having a traffic accident compared to those with an AHI  $\leq$  10. The increased risk persisted after statistically adjusting for the effect of potential confounding factors affecting traffic accident rates. Others have usually found that SAHS is associated with increased driving risk. However, increased risk was found only in those with severe disease (AHI>40) and then only mildly increased (1.5 times more accidents in SAHS with AHI>40) in one large study (n=460 patients matched to 581 controls) using ministry of transport accident rates (George & Smiley 1999).

Sleepiness at the wheel is estimated to cause about 20% of all road accidents (Horne & Reyner 1995). Further, driving accidents occurring because of falling asleep are usually at high speed, without avoidance reactions, and are associated with serious injuries and a high mortality rate (Horne & Reyner 1995). Although there are many causes of sleepiness, for example insufficient sleep due to shift work, SAHS is the most common medical condition causing sleepiness and there is effective treatment available.

### ***1.6.2 Mortality and vascular disease morbidity***

Early investigators (He et al. 1988) reviewed mortality in a group of untreated SAHS patients after 8 years and found that there was increased mortality in those with an AHI>20events/hr, compared to less than 20 events/hr. Others have confirmed this association and found that the mortality rate due to vascular disease is higher in conservatively treated patients (weight loss) than those having a tracheostomy (Partinen



et al. 1988). There may be selection bias in these studies as both are retrospective. Increased mortality in SAHS is postulated to occur mainly due to increased risk of cardiovascular/cerebrovascular disease. There has, however, been difficulty in establishing that SAHS is an independent risk factor for these diseases because of other potentially confounding risk factors. Male sex, increasing age, obesity, and smoking (Douglas & Polo 1994, Bloom et al. 1988) all predispose to SAHS but are also well known risk factors for vascular disease. Associations between SAHS and vascular disease may be due to such confounders rather than to the effects of SDB per se.

Early prospective questionnaire-based cohort studies found an increased incidence of ischaemic heart disease and stroke in community samples when subjects had frequent or habitual snoring compared to non-snorers. For example, in one study of middle-aged men habitual snoring compared to non-snoring was associated with odds ratios of 1.9 of ischaemic heart disease and 2.38 for development of ischaemic heart disease, stroke, or both (assessed from hospital records and death certificates) (Koskenvuo et al. 1987). In the above study an increased risk persisted after adjustment for BMI, hypertension, smoking, and alcohol use.

An increase of PSG-diagnosed SDB has been found in post-myocardial infarction males compared to matched normal controls, after allowing for common confounding risk factors for ischaemic heart disease (Hung et al. 1990). In a study of 128 patients with either stroke (n=75) or TIA the prevalence of SDB and SAHS was higher than in a matched control population (Bassetti C 1998). In this study, in which 80 of the

participants had a sleep study, 62.5% of the stroke/TIA patients had an AHI>10 compared with 12.5% of the controls. In both these studies matched controls may have included relatively 'healthy' subjects (rotary club members and "healthy volunteers", respectively), which may not be representative of others in the community. The high prevalence of SDB in TIA patients in the above study suggests that the SDB often precedes irreversible cerebral injury. Although a high prevalence of SDB in stroke has been found in a number of studies, it is still unclear if SDB is an independent risk factor for stroke.

Pulmonary hypertension in SAHS occurs in about 20% of patients, is generally mild and seems to need the co-existence of either chronic obstructive airways disease (not necessarily severe) and daytime hypoxaemia or marked obesity and daytime hypoxaemia (Weitzenblum et al. 1988).

In a 24-hour ECG study of 400 SAHS patients, with predominantly moderate to severe disease (in terms of AHI), Guilleminault and colleagues (Guilleminault et al. 1983) found an increased incidence of cardiac arrhythmias. Sinus arrest  $\geq 4$ seconds and extreme bradycardia  $<30$  beats per minute were found during sleep (8% and 7% of patients, respectively) and are not seen in 24 hour surveys of healthy subjects. After tracheostomy, in 50 of these patients, no patient had an arrhythmia other than isolated extrasystolic beats.

Currently, large prospective epidemiological studies are following community samples to determine the risk of cardiovascular morbidity from SDB. The Sleep Heart Health Study has analysed baseline cross-sectional data on 6,132 individuals and found an independently increased risk of hypertension (odds ratio = 1.37) with AHI >30 (compared to AHI<1.5events/hr) (Nieto et al. 2000). The Wisconsin sleep cohort has found there is a dose-response relationship between blood pressure and increasing AHI at baseline (Young et al. 1997a), and between AHI and subsequent development of hypertension after 4-8 year follow-up (Peppard et al. 2000). Lavie and colleagues have analysed data from their clinic population (2,677 patients) and found an independent association between AHI and hypertension (Lavie et al. 2000). Hence, there is good evidence that SDB is an independent risk factor for hypertension and therefore probably for cardio- and cerebro-vascular disease.

### ***1.6.3 Undiagnosed SAHS in the community***

Using the Wisconsin sleep cohort data, it is estimated that 80% percent of the middle-aged population with SAHS is undiagnosed (defined as daytime hypersomnolence often or almost always and AHI>5 or AHI>15) is over 80% (Young et al. 1997b). Assuming that SAHS diagnosed in community-based studies has the same pathophysiological consequences as that diagnosed in the clinic, then only a small proportion of the total disease burden is currently being assessed and treated. However, much of the disease found in community studies is relatively mild (in terms of AHI) and further work is needed to establish the health consequences of mild disease. The

Wisconsin cohort study found that there is a small increased risk of hypertension even with mild disease (i.e., AHI 0.1-4.9 compared to 0) (Peppard et al. 2000). Others (Hung et al. 1990) found an increased risk of ischaemic heart disease with mild SDB (AHI > 5).

#### ***1.6.4 Cost of diagnosis and treatment***

There is currently a high and increasing demand for sleep service facilities due to the high prevalence of sleep disorders, such as SAHS, and increasing public awareness of sleep problems. There has been little work done on the cost benefit of treating SAHS. However, in one study it was found that diagnosis and treatment of patients with SAHS results in a reduction in important healthcare costs compared to before diagnosis (comparison was made with a control group over the same 4 year period) (Bahammam et al. 1999).

**CHAPTER 2 - CPAP TREATMENT FOR THE SAHS**

## **2.1 Introduction:**

Before the use of CPAP treatment (1981), there were few treatment options available for patients with the SAHS. Clinical recognition of SAHS during this time was generally limited to those with severely symptomatic disease whom had severe daytime sleepiness and/or cardiovascular complications (many may also have had OHS). In the 1970's some of these patients were treated with a permanent tracheostomy, which was very effective (Coccagna et al. 1972) but was invasive and had serious cosmetic and other side effects. It was known that SAHS was related to obesity and another treatment option before 1981 was weight loss, in the obese SAHS patient. This conservative approach has limited effectiveness due to problems losing and maintaining weight loss (Noseda et al. 1996, Charuzi et al. 1992). Medications, including respiratory stimulants (e.g., progesterone) and antidepressants, had proved largely ineffective (Sullivan et al. 1981, Katsantonis et al. 1988) and are no longer indicated for the SAHS.

The discovery that continuous positive airway pressure to the upper airway, via a nose or face mask, (CPAP) controlled apnoeas/hypopnoeas and led to symptomatic improvement was a major advance in the treatment of SAHS. CPAP is now the main form of treatment for SAHS [Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnea syndromes. American Thoracic Society. Official statement adopted March 1994]. CPAP treatment is not, however, without problems and this has led to other treatment options being developed. The most important of these are mandibular re-positioning splints (MRS) and a variety of surgical treatments on the upper airway or the bony

structure supporting the upper airway. In this thesis only CPAP treatment will be discussed in detail but the role of other treatment options, in relation to CPAP, will be briefly reviewed at the end of this chapter.

## **2.2 Physiological mechanisms of CPAP treatment:**

### ***2.2.1 Effect on the upper airway***

CPAP is effective for SAHS, in large part, because of its ability to act as a pneumatic splint; preventing the passive collapse of the upper airway during sleep (Sullivan et al. 1981). Computerised tomography (CT) of one patient using CPAP during sleep showed that CPAP increased the size of the airway to larger than its (reduced) dimensions during the awake state (Rapoport et al. 1983). There appear to be effects of CPAP other than simple passive splinting. Patients on long-term CPAP treatment who temporarily stop treatment have some small reduction in their AHI (i.e., off CPAP) compared to the values before treatment, possibly due to decreased upper airway oedema (Kribbs et al. 1993a).

### ***2.2.2 Effect of CPAP on sleep architecture***

The first study of CPAP by Sullivan and colleagues described resolution of apnoeas and changes in sleep architecture after 5 severe (mean AHI=62/hr in NREM sleep) SAHS patients started CPAP. EEG arousals were abolished and there was less 'light' sleep (stage 1) and more deep sleep (stage 3 + 4) (Sullivan et al. 1981). There was also a 'rebound' reduction in the time between sleep onset and the onset of the



first period of REM sleep (REM sleep latency) and the amount of REM sleep was increased (Sullivan et al. 1981). All these changes were suggestive of 'better' sleep quality with CPAP, and reversal of sleep architecture disruption caused by SDB. Similar changes in the pattern of sleep architecture with CPAP have been seen in a number of 'before and after' studies, however, there have been no randomised controlled data confirming that CPAP improves objective sleep quality.

## **2.3 Practicalities of CPAP treatment:**

### ***2.3.1 Equipment***

During CPAP treatment patients are connected to a machine that provides continuous positive airway pressure to the upper airway during sleep. The main parts of a CPAP machine include a blower unit that is like a reverse vacuum cleaner and is able to provide high air flow at relatively low pressure (i.e., to compensate for inspiratory flow rates of 40-50 L/min and leakage). There is also a hose for the air to flow along and a nasal mask (or occasionally other interfaces, e.g., full-face mask or nasal prongs) with headgear to hold the mask in place (Sullivan et al. 1981). The mask needs to have a venting device to vent exhaled gases. Other common features include a ramping device that allows the pressure to build up slowly to the pre-set pressure over 5-20 minutes, as desired. Humidification and supplemental oxygen can be added into the inspired airflow. Recent developments allow the pressure to be automatically altered during the night, using microchip technology and an in-built system to assess the patient's breathing (Automatic or 'intelligent' CPAP). This means delivered pressure can be varied, for example in



response to changes in the patient's position (e.g., supine position requires higher pressures than the lateral position) and stage of sleep (e.g., stage REM sleep usually requires higher pressures than NREM) (Berthon-Jones 1993).

### ***2.3.2 Education***

Patients are advised to use CPAP treatment every night (and at all other times they sleep) and all night, except if they develop an upper respiratory tract infection or serious side effect of treatment. This requires regular commitment from patients to persist in spite of inconvenience, cosmetic considerations, and possible discomfort/side-effects. It would seem obvious that some education would be beneficial to patients starting CPAP treatment and that education may improve compliance. In most centres patients starting CPAP receive, at a minimum, explanation of the treatment by their physician. In one study the simple intervention of providing information about SAHS and CPAP treatment in a pamphlet was associated with improved objective compliance (Chervin et al. 1997) compared to a control group with no intervention. The first month of CPAP treatment seems to be important in determining later compliance (Kribbs et al. 1993b) and in the above study (Chervin et al. 1997) there was evidence suggesting that educational interventions are more effective at that time than later on. Telephone advice and encouragement have not been shown to help, but numbers in the intervention groups in these studies were small [n=10 (Fletcher & Luckett 1991), n=12 (Chervin et al. 1997)]. There are uncontrolled retrospective data suggesting that group education sessions may improve CPAP use (Likar et al. 1997). The optimal amount of education is unknown although in one randomised controlled trial intensive

education/support led to better CPAP use and greater improvement in symptoms, mood, and reaction times than standard education (Hoy et al. 1999).

### ***2.3.3 CPAP titration***

Patients are usually prescribed a single CPAP pressure, which is determined by a procedure called CPAP titration in the sleep centre. During pressure titration the minimum pressure that controls apnoeas, hypopnoeas, loud snoring, and minimises EEG arousals is determined. The pressure needs to control these respiratory events during the supine and the prone position, and in REM as well as NREM sleep. This pressure can be determined 'manually' by slowly increasing the pressure and then decreasing it again until a satisfactory pressure is found. Flattening of the flow contour is a sign of less apparent SDB, called flow limitation, that may also disrupt sleep (Montserrat et al. 1995, Rapoport 1996). Currently, in some centres, the titration pressure is determined automatically, using CPAP machines with an inbuilt system to detect increased airflow resistance, hypopnoeas and apnoeas (Teschler et al. 1996).

### ***2.3.4 Side effects***

Side effects from CPAP treatment are common but are rarely severe. The commonest side-effects reported by patients after a mean of 19 months of CPAP treatment in one representative study (Pepin et al. 1995) were nasal side effects (dryness of nose and mouth=65% or congestion=25%) and problems from the mask abrading the face (approx. 30%) or causing local allergy (approximately 10%). Also

inconvenience from the treatment was commonly reported; noise was reported to cause inconvenience by 34% of patients (and noise by 50% of spouses in the above study) and bulkiness of the machine by 20%. There are case reports of massive epistaxis (Strumpf et al. 1989), atrial irregularity (bigeminy) (Meurice et al. 1992), pneumocephalus (Jarjour & Wilson 1989), and meningitis (Bamford & Quan 1993) with CPAP treatment. In these reports, however, there were usually other aggravating factors (e.g., massive epistaxis with coagulopathy, meningitis with sinus mucocoele) and a causal link was likely but not proven. There are no absolute contraindications to CPAP treatment but relative contraindications are bullous lung disease (even though there have been no reports of pneumothorax complicating CPAP) and recurrent sinus or ear infections [Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnea syndromes. American Thoracic Society. Official statement adopted March 1944].

### ***2.3.5 follow-up***

After starting CPAP treatment follow-up is necessary, particularly in the first few months, to troubleshoot problems such as nasal irritation/congestion, skin abrasion/pressure areas, and mask fitting difficulties. Some long-term follow-up is also advisable. Problems can occur after the early months of treatment, for example, due to lack of efficacy in the case of the patient gaining weight (i.e., may require higher CPAP pressure) or rare complications such as severe epistaxis (Strumpf et al. 1989). Compliance with CPAP treatment should be objectively monitored using in-built time clocks [Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnea syndromes. American Thoracic Society.

Official statement adopted March 1944]. This will allow early identification of problems which can be addressed and this may result in better CPAP use (Krieger & Kurtz 1988). Replacement parts for wear and tear or breakages of equipment may also be needed.

#### **2.4 Efficacy of CPAP treatment:**

To physicians working in the field of sleep medicine the effectiveness of CPAP on SAHS symptoms is clear, and sometimes dramatic, for many patients. However, others outside the field have questioned the beneficial effects of CPAP (Wright et al. 1997). Partly in response to this criticism, a number of randomised controlled trials of the effectiveness of CPAP have been reported in the past 6 years. These studies have shown that CPAP is effective in improving sleepiness, cognitive function, psychological well being, and quality of life (when compared with an oral placebo or sham CPAP) (Engleman et al. 1994a, Engleman et al. 1997, Engleman et al. 1998, Engleman et al. 1999, Jenkinson et al. 1999, Redline 1998a). In view of improvements in vigilance and other cognitive functions with CPAP it is perhaps not surprising that a randomised controlled study found that in SAHS CPAP improves driving performance on a driving simulator (Hack 2000). There is supportive evidence from observational studies that CPAP reduces driving accidents (Horstmann et al. 2000). There are randomised-controlled data showing an improvement in nocturnal blood pressure (but not daytime blood pressure) from CPAP treatment (Dimsdale et al. 2000). There have been no randomised data showing that CPAP improves objective sleep quality.

## **2.5 Compliance with CPAP treatment:**

### ***2.5.1 Compliance with medical treatments***

As with all beneficial medical treatments, benefit depends to some degree on patient compliance with the prescribed treatment. Compliance also has important health-economics implications. For example, a study that found a reduction in healthcare costs after diagnosis and treatment of SAHS patients with CPAP (Bahammam et al. 1999) also found this reduction was only in the sub-group who reported being compliant with CPAP treatment. A wide range of compliance with medical treatment has been reported for different treatments, using different compliance outcome measures; however, compliance levels between 29% and 59% are usually reported (Griffith 1990). Partly because of these generally poor levels of compliance to medical treatments there has developed a large research literature examining the factors affecting compliance and ways of improving compliance.

Studies have shown that physicians cannot predict who will be compliant with medical drug prescriptions any better than chance alone (Mushlin & Appel 1977). A number of factors have been identified that influence compliance with medical treatment. These factors can be conveniently grouped as follows: 1) patient behaviour, 2) the behaviour of the doctor, 3) the type of illness, and 4) the nature of the treatment.

Factors affecting patient behaviour include such variables as demographic factors (e.g., age; elderly comply less well), psychological factors (e.g., paranoid

personality traits are associated with worse compliance), and the patient's health belief model (Griffith 1990). The behaviour of the doctor is important (informal and friendly improves compliance) and even the setting is important (e.g., day care is associated with better compliance than outpatient care) (Griffith 1990). The above factors apply generally to most medical treatments and it is important that doctors are aware of them. However, detailed studies are needed to identify what are the important factors for a given disease and treatment.

### ***2.5.2 Compliance with CPAP treatment for SAHS***

CPAP is a mechanical treatment and so some of the factors affecting compliance with CPAP may be different from those affecting compliance with a medication. Identifying the variables influencing compliance specific to CPAP treatment (for SAHS) are most likely to be useful for decision making in the normal clinical setting. The predictive role that patient-related, disease-related, and treatment-related variables have on CPAP use in the SAHS will be examined in detail in this thesis.

### ***2.5.3 Subjective versus objective assessment of CPAP use***

CPAP use can be measured subjectively or objectively. Subjective use is assessed from patient-report or questionnaires given at clinic or over the phone. Objective measurements make use of monitors built into the CPAP machine. Early studies measured subjective compliance, mainly by retrospective questionnaire (Hoffstein et al. 1992, Sanders et al. 1986, Waldhorn et al. 1990, Rolfe et al. 1991, McEvoy &



Thornton 1984, Sullivan et al. 1984). These studies suggested that long-term use [longest mean (+/-sd) follow-up = 17 (+/-11) months (Hoffstein et al. 1992)] was probably over 70%. Further, most of these patients [96% in one study (Waldhorn et al. 1990)] reported using CPAP every night and for all (or nearly all, i.e., minus 1-2 hrs) their sleep time. However, they were based on retrospective questionnaire data without objective confirmation of use and were likely to have had significant selection bias. Hoffstein and colleagues found that 82% of those that replied to questionnaires were still using CPAP whereas only 32% were still using CPAP among those that did not reply but were then phoned (Hoffstein et al. 1992). Further, it has since been shown that subjective CPAP use data overestimates CPAP use determined objectively from in-built time clocks in direct comparisons of the same group of patients (Rauscher et al. 1993, Kribbs et al. 1993b).

There are 2 types of in-built time clocks, the commonest of these measures 'run time', i.e., the total time that the CPAP machine is switched on. Some monitors also measure 'pressure time', that is the total time that the CPAP machine operates at the prescribed pressure. The pressure time is the most accurate measure of the time that a patient receives the treatment as prescribed and there are no errors due to the machine being left on (accidentally or deliberately) when not used. However, a number of studies have shown a strong correlation between the run time and pressure time (Engleman et al. 1994b, Reeves-Hoche et al. 1994, Kribbs et al. 1993b). Further the difference between the two measures is small (a correction factor of 0.9 converts the run time to pressure time (Engleman et al. 1994b, Reeves-Hoche et al. 1994, Kribbs et al. 1993b). The lower time at pressure seems to be due

to leak rather than deliberate running of the machine without using it (Kribbs et al. 1993b).

#### *2.5.4 Measures of CPAP use*

There are a number of different ways of measuring compliance with CPAP. Some important assessments that are commonly used are as follows:

- 1) CPAP acceptance (also called primary compliance) (%) = the percentage of patients who are prescribed CPAP by their physician that subsequently take CPAP with them for home use. CPAP acceptance can be further sub-divided. There are those who, in the clinic, decline a CPAP titration night (i.e., are never booked for CPAP titration), those that are booked for CPAP titration but don't attend, and those that are unable to tolerate CPAP on the titration night and so don't take CPAP home.
- 2) Average nightly CPAP use (hrs/night) = the average use of CPAP per night estimated by the patient (subjective) or calculated from an in-built time clock/monitor as the total time CPAP is used divided by the number of nights the patient has had the CPAP machine (objective).
- 3) Long-term CPAP use (%) = the percentage of patients who continue using CPAP over time. The methods of survival analysis [e.g., that of Kaplan-Meier (Altman 1991)] are often used to analyse and draw plots of the percentage still using CPAP versus time.



CPAP acceptance is an important but often forgotten measure. If it is not included in the assessment of compliance with CPAP treatment there is an artificially high figure for overall compliance. For example, in one study 76% of patients who started CPAP continued treatment at a mean ( $\pm$ sd) of 14 ( $\pm$  10.7) months follow-up, but overall compliance at follow-up is only 63% if non-acceptance is taken into account (Waldhorn et al. 1990). The percentage of patients that decline a CPAP titration night recommended by their physician in the clinic is usually unknown. The only study that gives a figure for this is by Rauscher and colleagues (Rauscher et al. 1991a) with 68% agreeing to a CPAP titration night. However, in that study treatment was recommended to all clinic patients with an AHI>15 regardless of symptoms; this is not an approach used in routine clinical practice. This data may be more relevant in the future if evidence from cardiovascular morbidity studies shows the level of SDB is an important predictor of morbidity, when CPAP treatment may be recommended for patients based on AHI and risk factors for cardiovascular disease (rather than symptoms) alone.

The average CPAP use per night gives a single measure of the usual duration of use each night. However, the use per night necessary to gain benefit is unknown. On theoretical grounds physicians advise patients to use CPAP every night and all night. This is based on the assumption that sleep quality can be disrupted by apnoeas and hypopnoeas at any time of the night (even after a period of CPAP use within a night (Rauscher et al. 1991b). Hence, using CPAP during all sleep will prevent this happening and achieve optimal sleep quality and oxygenation. In one randomised-controlled study an average ( $\pm$ sd) nightly use, at the correct pressure, of only 3.4 ( $\pm$ 0.4) hours/night was associated with benefit in sleepiness, cognitive

function, and quality of life (Engleman et al. 1994a). There is one recent study by Stradling and colleagues (Stradling & Davies 2000) with assessments analogous to 'dose-response' studies used for medications which supports a direct relationship between increased nightly CPAP use and benefit from CPAP. These authors have suggested that measures of benefit, such as change in the ESS with treatment, may be a more appropriate measure than average nightly CPAP use (Hardinge et al. 1995).

A further problem with the average nightly CPAP use as a measure of compliance is that as a single measure it may hide irregular CPAP use. In a study by Kribbs and colleagues (Kribbs et al. 1993b) the pattern of CPAP use over time was studied and only 46% of patients were considered to be regular users; defined as using CPAP at least 4hrs/day on at least 5 days per week. The average nightly use in this study was 4.9 hrs/night for those nights where use was attempted. Attempted use only occurred on 68 of 106 nights, so the (unreported) average nightly use for the study period is about 3.2 hrs/night, suggesting the 35 patients studied were quite a poorly compliant group.

Irregular use seems to have clinical consequences according to the above researchers. In a separate study they found that, for patients who were established on CPAP, 1 night without treatment returned patients to their pre-treatment objective sleepiness level (MSLT) and reaction time (Kribbs et al. 1993a). This latter study may be criticised because compliance with treatment was uncertain (mainly subjective confirmation of CPAP use and MSLT scores were abnormal on

CPAP) and there was no blinding (i.e., patients might have expected themselves to be more sleepy after a missed treatment night).

From the early days of CPAP treatment there has been concern that many patients would not use CPAP in the long-term (Sullivan et al. 1981). As SAHS appears to be a lifelong condition (Guilleminault et al. 1981) and CPAP treatment is not curative (Kribbs et al. 1993, Nosedá et al. 1996) it is clearly important that CPAP use is continued long-term. Many of the studies of long-term use have relied on subjective data (Hoffstein et al. 1992, Sanders et al. 1986, Waldhorn et al. 1990, Rolfe et al. 1991, McEvoy & Thornton 1984, Sullivan et al. 1984). Of those using objective data (Krieger et al. 1996, Krieger & Kurtz 1988, Meurice et al. 1994) only one study could be found (Medline and Embase) that followed up more than 50 patients for a mean follow-up time of over 1 year (Krieger et al. 1996). In view of this lack of adequate long-term CPAP use data we have examined a large cohort of SAHS patients followed for up to 139 months, median 22 months, described in chapter 4 of this thesis.

As discussed in chapter 1.4.7 there is a consistent body of literature showing that in SAHS daytime sleepiness, cognitive dysfunction, and impaired vigilance are related to brief arousals from sleep. But impairment of daytime function (objective measure of sleepiness; MSLT) in SAHS is also related to changes in sleep architecture (including stage 1, stage 3+4, stage REM sleep, and total sleep time). Further, although the relationship between arousals and CPAP use and benefit has been well studied there is little work on other sleep architecture variables and CPAP use and benefit. The factors determining CPAP use and benefit are poorly understood and

the possible role of sleep architecture changes with CPAP has been investigated in this thesis (chapter 6).

## **2.6 Other treatments used for SAHS:**

### ***2.6.1 Weight loss***

Although reported rarely, case reports confirm cure can occur due to weight loss (often undertaken during CPAP treatment), with a follow-up time of up to 11 months in one study (Aubert-Tulkens et al. 1989). One study examined the effectiveness of CPAP treatment and weight loss to wean 95 unselected SAHS patients from CPAP (Nosedá et al. 1996). The above study used a pragmatic approach to weight loss with patients attempting to lose weight either by their own means, with the help of a dietician, or with bariatric surgery (e.g., gastroplasty operations, offered to those with BMI > 40). Follow-up PSG sleep studies off treatment were performed, after 1 year on CPAP with attempted weight loss, in 39 'CPAP compliant' patients. Four patients had a follow-up AHI<10; 2 of these were successfully weaned from CPAP (defined as an AHI<10 while still off treatment 2 weeks later) and a further 2 who asked to be weaned were weaned with a follow-up AHI=10-20 events/hr. Surgical treatment (Roux-en-Y gastric bypass or vertical banded gastroplasty) for morbid obesity in 47 SAHS patients who had repeat sleep studies at 1 year, resulted in a reduction of mean AHI from 60 to 8 events/hr and 72% had an AHI<10 (Charuzi et al. 1992). At 7 years, 22 of 44 patients completing questionnaires had regained excess weight. 6 patients had been restudied at 7 years; 3 had an AHI<20 but another 3 had regained large amounts of weight and all these

had an AHI > 45 events/hr. The authors concluded that long-term follow-up is needed and patients need to be forewarned about the recurrence of SAHS if weight is regained. The operative mortality in one series of 126 patients with SAHS and/or OHS was 4%; this was higher than those who had similar surgery (0.2%) for obesity without SAHS and/or OHS (Sugerman et al. 1992). In spite of the low cure rate of weight loss it is important to strongly advise weight loss as an adjunct to CPAP treatment, for its other health benefits as well as the possibility of cure of SAHS.

### ***2.6.2 Upper airway and maxillofacial surgery***

There are problems with the literature on surgical treatment of SAHS that make it difficult to determine the effectiveness of surgical procedures and to define who is likely to gain benefit (Pepin et al. 1996). These include a relative paucity of studies where established treatments are used as a control group and the use of different criteria for effectiveness than is used for CPAP. For example, a 'good' response to uvulopalatopharyngoplasty (UPPP) occurred in 37 of 122 patients in one study (Katsantonis et al. 1988). However, this was defined as a 50% reduction in AHI rather than a reduction to normal levels (usually defined as AHI < 5 or < 10 events/hr slept) and/or resolution of symptoms.

In part because there are usually multiple anatomic sites of obstruction in SAHS patients, it has been difficult to identify the small sub-group of SAHS patients that may benefit from UPPP. Some success has been reported with the use of a technically difficult procedure of determining closing pressures by fiberoptic



pharyngeal endoscopy during sleep (Morrison et al. 1993). In the above study this procedure was performed in only 15 patients that then had UPPP. Improved AHI occurred in 3 of 4 patients who had exclusively nasopharyngeal collapse (but 1 still had AHI of 27) and no one improved among 9 patients with sites of collapse at, but not exclusive to, the nasopharynx (Morrison et al. 1993).

The low success rate of UPPP in controlling SDB appears to have consequences on mortality because UPPP patients had the same mortality as untreated patients with  $AHI > 20$  (and higher than CPAP or tracheostomy patients) in one retrospective longitudinal study (He et al. 1988). Others have contested this association (Lysdahl & Haraldsson 2000). As some UPPP patients may need CPAP therapy to adequately treat SDB it is of concern that they have mouth leak and intolerance of CPAP at relatively low pressures [mean ( $\pm$ sd) leak and intolerance pressure 6.8 ( $\pm$ 2.4), 14.5 ( $\pm$ 2.6) cm H<sub>2</sub>O, respectively] (Mortimore et al. 1996). UPPP patients who are treated with CPAP have a lower nightly CPAP use (Mortimore et al. 1996) and worse long-term use (Waldhorn et al. 1990) than routine clinic patients. However, the worse long-term use may be because these patients also were less sleepy prior to treatment (Waldhorn et al. 1990).

Maxillofacial surgery includes a number of different types of operation, from relatively minor (e.g., UPPP plus geniotubercle advancement) to more complex operations such as maxillo-mandibular advancement osteotomy (MMO). There has been one controlled study comparing MMO with CPAP, in the same patient (fixed order), which found that MMO, on selected patients, is as effective as CPAP in improving vigilance, RDI, and sleep architecture (Conradt et al. 1998). These

operations are performed in few centres and have not been widely used perhaps because of their complexity and expense.

### ***2.6.3 Oral appliances***

The term 'oral appliances' refers to a number of different types of appliances placed in the mouth that may reduce the sleep-induced narrowing in the upper airway. The most common type of these are the mandibular repositioning splints (MRS) which attach to the dental arch (usually via the teeth) and push the mandible forward and/or downward. This increases the superior airway space and possibly reduces the compliance of the upper airway (Schmidt-Nowara et al. 1995). These devices are usually fitted individually by an orthodontist or dentist. Most studies of MRS devices are 'before and after' studies and there are no published randomised placebo controlled studies of MRS devices at this time (but there are studies with non-placebo controls – below). One study compared PSG changes within patients when using the MRS compared to not using it by studying 51 patients on a single night, with one half of the night with the device and the remainder without (in random order) (O'Sullivan et al. 1995). In the above study there was a mean reduction of AHI from 32.2 to 17.5 events/hr while using the MRS (39 patients had SAHS and had MRS because they could not tolerate CPAP). There were also improvements in sleep architecture and arousal frequency. In the above study (O'Sullivan et al. 1995) the percentage of patients who had an AHI<20 on treatment was 70% for those with pre-treatment AHI=20-60, but only 22% for those with a pre-treatment AHI>60. This study is consistent with other studies showing that MRS devices do improve SDB in most patients with SAHS, but in many patients

there is inadequate control of SDB, particularly in the more severe groups. Randomised controlled studies comparing MRS to CPAP, show that MRS is less effective at controlling SDB than CPAP but patients prefer to use MRS over CPAP (Ferguson et al. 1996, Ferguson et al. 1997). In some patients MRS leads to worsening of SDB, suggesting that follow-up PSG may be needed in selected patients (Ferguson et al. 1997).

Side effects from using a MRS consist of initial discomfort and excess salivation and long-term effects of temporomandibular joint discomfort, possible dental damage, and periodontal disease. In one study in which patients were re-examined at a mean ( $\pm$ sd) of 31 ( $\pm$ 18) months 15/106 (14%) had occlusal changes (comparing new bite registration with original bite registration). These occlusal changes were reversible with appropriate exercises and the authors advised regular monitoring (6 monthly) in such patients (Pantin et al. 1999). Although tolerance of the MRS seems to be better than that of CPAP, the long-term compliance with MRS devices is still uncertain. In one study with complete follow-up questionnaire responses for 68 patients fitted with an MRS, 75% reported still using the device at a mean follow-up of 7 months and most reported using it for the entire night nearly every night (Schmidt-Nowara et al. 1991). There are no objective MRS use data and such subjective reports are likely to be overestimates, judging from the CPAP literature.

Overall, these devices appear to have a role for simple snorers, for patients with mild SAHS or in those patients who are unable to tolerate CPAP treatment. Further work is needed to determine who is likely to have effective control of SDB with



MRS, and to assess long-term use with objective measures such as by covert monitors that sense body heat.

## **2.7 Aims of this thesis:**

As I have outlined, in these first 2 chapters, SAHS is a common problem with widespread consequences. It is likely that most cases of SAHS in the community are undiagnosed and untreated and there is a need for more expeditious ways of assessing and treating patients, such as by split-night studies. CPAP is the main treatment but its major limitation is poor patient compliance. Factors that are important in predicting CPAP use are poorly understood, and there is a lack of objective data on long-term CPAP use.

Although CPAP controls SDB and reduces EEG arousals, improvement in the patient's sleep quality has never been shown in a randomised placebo controlled study. There is also a paucity of data on the relationship between CPAP treatment effects on objective sleep quality and CPAP use and benefit. Partners of patients with SAHS are often more aware of the patient's nocturnal symptoms than the patient. The effect of CPAP on objective sleep quality and quality of life of partners has never been assessed in a randomised placebo controlled trial.

The aims of this thesis, therefore, were to investigate the usage, administration and benefits of CPAP therapy. Specifically they were:

Firstly, to investigate CPAP use, particularly long-term use, in a large clinic population and determine clinically useful predictive factors. Secondly, to examine

the long-term outcome of CPAP therapy in patients managed using split-night CPAP studies by carefully matching them with patients managed following a full diagnostic night on important baseline predictors of long-term use. Thirdly, to examine the effect of CPAP on the patients' and their partners' sleep architecture in a randomised placebo controlled study. Finally, to explore relationships between CPAP use (and benefit from CPAP) and the sleep quality of the patient and their partner. Chapters 4-6 present the results of studies addressing these aims.

# CHAPTER 3 – METHODS

### **3.1 Introduction:**

Much of the work in chapters 4 and 5 of this thesis involved the construction and interrogation of a database of all patients booked for CPAP treatment at the Scottish National Sleep Centre from January 1986 through to February 1997. The next 2 sections of this chapter detail the routine management of patients booked for CPAP treatment and how a database of this management was constructed.

In the study described in chapter 6 the main outcome measure was objective sleep quality (among patients and their partners). Polysomnographic assessment of sleep quality, with particular reference to home monitoring, will be described in this chapter. Finally, the questionnaires and other assessments used will be described.

### **3.2 Outline of management of SAHS at the Scottish National Sleep Centre:**

#### ***3.2.1 diagnosis***

Patients were evaluated for possible SAHS by clinical interview and examination with involvement of a physician experienced in sleep medicine. Results of an overnight sleep study as well as pulmonary function tests, chest X-ray, and at times other investigations such as a multiple sleep latency test (MSLT) were reviewed prior to deciding on the need for CPAP treatment. The decision to treat with CPAP was based on the presence of at least two major symptoms of the SAHS (Whyte et al. 1989) and an appropriate sleep study where there was an abnormal frequency of apnoeas and hypopnoeas.

Diagnosis of SAHS was usually with full PSG sleep studies. Full PSG recorded sleep-related and cardiorespiratory signals. Sleep-related signals were recorded using silver chloride electrodes. According to the international 10/20 electrode placement system (Cooper et al. 1980), surface bipolar EEG signals were recorded from Cz and Pz with a common Fpz grounding electrode. Right and left electroculography (EOGs) were recorded from the outer canthus of each eye (Fp1 and Fp2). Mixed EEG/EOG signals, from Cz/Fp1 and Cz/Fp2, were recorded to better monitor frontal EEG. Bilateral submental electromyography (EMG) electrodes recorded activity from the submental muscles. Leg EMGs were recorded from anterior tibialis muscles. Cardiorespiratory signals were: "airflow" by a triple oronasal thermistor on the upper lip, chest and abdominal excursions by inductance plethysmography, and 2-lead electrocardiogram. Oxygen saturation was recorded using an Ohmeda 3700 (Ohmeda, Louisville, Colorado, U.S.A.) oximeter by finger or ear probe. Other signals were body position using a mercury switch and snoring sounds by a microphone in the headboard. Limited sleep studies, that recorded cardiorespiratory signals but not EEG, were increasingly used towards the end of this period. Limited studies included the AutoSet diagnostic (ResMed Ltd., North Ryde, NSW, Australia), EdenTec (EdenTec Corp., Eden Prairie, MN, U.S.A.) systems, and overnight oximetry was also used.

Apnoeas were defined as the absence of oronasal airflow in the presence of thoracoabdominal movement for at least 10 seconds. Apnoeas were considered to be obstructive if there was detectable thoracoabdominal movement, central if there was no detectable thoracoabdominal movement, and mixed if there was initially no

thoracoabdominal movement but movement commenced during the apnoea. Hypopnoeas were defined as a reduction in thoracoabdominal movement of at least 50% of the baseline (determined from the previous 2 minutes) for a minimum of 10 seconds.

The AHI equaled the sum of apnoeas and hypopnoeas per hour of sleep. The cutoff for an abnormal AHI warranting treatment, when accompanied by appropriate symptoms, has varied over the study period but has always been between over 5 or over 15 events/hr slept. Diagnosis based on limited sleep studies required an apnea/hypopnoea score > 30 events/hr in bed (Whittle et al. 1997, Rees et al. 1998).

### ***3.2.2 CPAP titration and education***

In most cases, if a diagnostic study confirmed SAHS patients were booked to spend a second night in the sleep centre to determine the appropriate pressure needed to control their SDB; i.e., for CPAP titration. In some cases patients were booked for a split-night study, in which case if there was an appropriate level of SDB during the first half of the night, CPAP titration was accomplished in the remainder of the night (chapter 1.5.2). Most CPAP titration was performed manually, to obtain the minimum pressure that normalized breathing pattern and minimized EEG arousals (Engleman et al. 1994b). Latterly, the AutoSet (ResMed Ltd., North Ryde, NSW, Australia) system was used to determine the pressure that controlled 90% of apnoeas, hypopnoeas, and flow-limited breaths. AutoSet CPAP titration is effective in controlling SDB among patients with SAHS (Teschler et al. 1996). CPAP machines were provided free of

charge to patients. Since 1990 all patients have been issued with CPAP machines with in-built time clocks that record the time the machine is switched on.

All patients received education prior to a CPAP titration night. This involved an explanation of the treatment by a specialist CPAP nurse, mask fitting from a wide range of more than 20 mask types, an educational video, and 20 minutes spent acclimatizing to CPAP on a bed during the daytime.

### *3.2.3 follow-up*

During the first 2 weeks after taking CPAP home patients were usually contacted by the nurse specialists, on one occasion. Sometimes, additional calls were made if there were ongoing problems. The average duration of these phone calls was approximately 10-15 minutes. Patients were asked about the effect of treatment on nighttime and daytime disease symptoms, then difficulties with use of CPAP were sought. Interface problems were addressed by changing mask type or headgear. The mask types most commonly used were the Respironics mask (Respironics, Marysville, PA, U.S.A.) in about 2/3 of patients and the Sullivan Bubble mask (ResMed Ltd., North Ryde, NSW, Australia) in almost 1/3. An Adams circuit (Mallinckrodt Ltd, St. Louis, MO, U.S.A.) was used in 32 patients to provide relief to skin pressure areas (especially to the bridge of the nose) or when patients disliked masks. Only 12 patients continued Adams circuits long-term. Full-face masks were used in fewer than 10 patients. Nasal/oral symptoms were treated with topical decongestants, with humidifiers, or with a chin strap (antihistamines were not used). Patients were reviewed in the sleep center by nursing staff if problems could



not be resolved by phone. Further support was available by a 24-hr telephone (messages recorded after hours) advice line run by the CPAP nurse specialists.

Clinic follow-up occurred initially within 3 months of starting CPAP. Subsequent reviews became less frequent as patients were established on treatment, with a maximum of 12 months between reviews. At each review patients were assessed clinically and the CPAP time clock was read to compute the average nightly use. Patients whose objective CPAP use was < 2 hours at any clinic appointment were confronted with their usage data and encouraged to increase their CPAP use. Any problems with CPAP side effects were addressed and a one-month review appointment made. If subsequent use was still <2 hours the CPAP machine was then reclaimed by the sleep center.

### **3.3 Construction of database of all patients booked for CPAP treatment:**

Data were obtained from review of all clinical records, patient and partner questionnaires (completed at the time of the original consultation – see appendix a, some minor modifications made over the study period), sleep study results, and objective CPAP use records during the above study period. A proforma was designed so that data were recorded about each patient booked for CPAP treatment in a standardized manner. We were interested mainly in compliance with CPAP treatment and the determinants of that compliance. The determinants of compliance that we considered were important were known indices of disease severity (e.g., AHI), common treatment-related variables (e.g., CPAP pressure), and commonly used patient-related variables (e.g., age). These variables were chosen since they are, in the



main, specific to sleep apnea and likely to be useful for decision making in the clinic setting.

Patients with kyphoscoliosis or neuromuscular disorders were excluded. Patients with SAHS and co-existing chronic obstructive airways disease were not excluded if CPAP alone was the modality of treatment chosen.

### **3.4 Assessment of sleep architecture:**

#### ***3.4.1 Overview***

Sleep architecture was described using rules set out by Rechtschaffen and Kales (R & K rules) in 1968 (Rechtschaffen & Kales 1968). The sleep study is divided into 30-second epochs or 'pages' and a score is given for each page. The score for a given page is the predominant sleep stage for that page (e.g., if there are two stages on a page the stage that lasts more than 15 seconds is scored).

Sleep must be distinguished from wakefulness. During wakefulness (stage wake) there are higher EEG frequencies [in the alpha (8-13 Hz) or beta ranges (>13 Hz)], usually there is elevated EMG activity, and eye blinks (binocularly synchronous). The total time spent asleep is called the total sleep time (TST), which is distinguished from the total time of the study, usually called the total recording time (TRT). The sleep efficiency index (SEI) reported in this thesis was defined as the TST divided by the TRT multiplied by 100 (to obtain a percentage). Sleep is

divided into two main types: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep.

### ***3.4.2 NREM sleep stages***

NREM sleep can be thought of in simple terms as a relatively inactive brain with a relatively active body. In NREM sleep the EEG frequencies become slower with increasing depth of sleep.

The “lightest” sleep is called stage 1 and is a transitional stage of sleep. The EEG is relatively low voltage, mixed frequency usually in the theta (2-7 Hz) range. The EEG may have characteristic ‘vertex sharp waves’. There may be slow rolling eye movements seen on the EOG signal.

Stage 2 sleep is characterised by ‘sleep spindles’ (short bursts of fast activity, 12-15 Hz, lasting >0.5 seconds) and ‘K complexes’ (a negative sharp wave, immediately followed by a positive deflection). There is a background of low voltage mixed frequency EEG. In our laboratory the onset of sleep is defined as the first page of stage 2 sleep.

Stage 3 and stage 4 are often grouped together and called ‘slow wave sleep’ (SWS). Both are defined by the presence of runs of large amplitude slow waves at <2 Hz. Stage 3 sleep is scored if more than 20%, but less than 50%, of a page consists of slow waves. Stage 4 is scored if more than 50% of the page is slow waves.

### ***3.4.3 REM sleep***

REM sleep can be thought of in simple terms as a state of sleep with an active brain but an inactive body. That is, the EEG is similar to wake, with a lot of fast activity (a few cycles per second slower than the awake state) and variable frequencies but the EMG (submental and postural) is at its lowest level for a given individual. It is also characterised by rapid eye movements (binocularly synchronous) readily seen on the EOG channels. There may be distinctive ‘saw tooth’ waves on the EEG.

### ***3.4.4 EEG arousals***

The R & K rules only recognise arousals from sleep that are associated with > 15 seconds of stage wake. There have been a number of definitions developed identifying shorter arousals that are physiologically important in SAHS (Stepanski et al. 1984, Martin et al. 1997b) but are not assessed by the R & K rules, so-called ‘microarousals’. The in-house Cheshire definition of microarousals (Martin et al. 1997a, Cheshire et al. 1992) was used in all scoring of arousals in this thesis. This defines an arousal as a return of EEG frequencies to alpha or theta for at least 1.5 seconds associated with a transient rise in EMG activity, no matter how brief. The arousal index reported in this thesis is the number of arousals/hr of sleep.

## **3.5 Reproducibility of sleep architecture scoring:**

The main outcome measure in chapter 6 is sleep architecture. Although scoring of sleep studies follows the rules set out by Rechtschaffen and Kales, there is a degree

of subjectivity in the assessments. Variability in sleep scoring can result from variation in the quality of the sleep studies and variability in recognising EEG patterns within and between scorers. To assess the accuracy of sleep scoring 8 randomly selected sleep studies were scored by the researcher and compared with the scoring of the senior technician. To assess reproducibility a further 8 randomly selected studies were scored twice by the researcher. In these inter-rater and intra-rater analyses the researcher was blind to the patient details and original results of the comparison studies. Intra-rater comparisons were made 6-12 months after the initial study was scored.

The results of the inter-rater and intra-rater studies are shown in table 3.1. Spearman rank correlations were used for these small sample data. Correlations were high, with  $r$  values  $\geq 0.79$  ( $p \leq 0.02$ ). The mean ( $\pm$ sd) of the difference of scores is also shown and is small, particularly for intra-rater data. For example, the lowest correlation between scores in the intra-rater comparison was for arousal index, but 95% of these scores differed by  $< 6.5$  events/hr. The SEI and arousal index data were pooled and are shown graphically in figures 3.1 – 3.4. Figures 3.1 and 3.2 show the data as a standard scatter plot of score 1 against score 2, with the line of identity superimposed. Figures 3.3 and 3.4 show results for the same data as a Bland Altman plot. Bland Altman plots give a better representation of the reproducibility of 2 sets of scores. These plots show small differences between scores, although the differences appear to be greater at the lower end of the average score range. This may be because arousals are easier to identify when disease is

severe. By contrast, severe disease means that patients have fragmented sleep and SEI may be less reliably scored.

Table 3.1

Reproducibility of sleep architecture variables

Sleep variable	Score 1, median (IQR)	Score 2, median (IQR)	r-value	Mean (sd) score difference score 1– score 2
<b>Inter-rater reproducibility</b>				
SEI, (%)	80.5 (60-87)	83.4 (61-90)	0.95**	-2.0 (3)
Arousal index, (events/hr slept)	26 (17-43)	23.2 (16-38)	0.95**	2.9 (2.7)
Stage 3+4, (mins)	71 (33-96)	55 (35-75)	0.93**	9 (13)
Stage REM, (mins)	60.2 (43-82)	66 (45-97)	0.81*	-6.3 (10)
<b>Intra-rater reproducibility</b>				
SEI, (%)	82 (69-87)	81.6 (66-87)	0.99**	0.6 (1.3)
Arousal index, (events/hr slept)	20.4 (18-37)	23 (18-34)	0.79*	0.2 (3.3)
Stage 3+4, (mins)	46 (26-65)	46.2 (28-61)	0.95**	-0.1 (5.3)
Stage REM, (mins)	103 (67-116)	102.5 (73-112)	0.93**	2.2 (7)

\*  $p \leq 0.02$ , \*\*  $p \leq 0.001$

Figure 3.1: Scatterplot of the relationship between first and second sleep efficiency index scores for all 16 rescored records

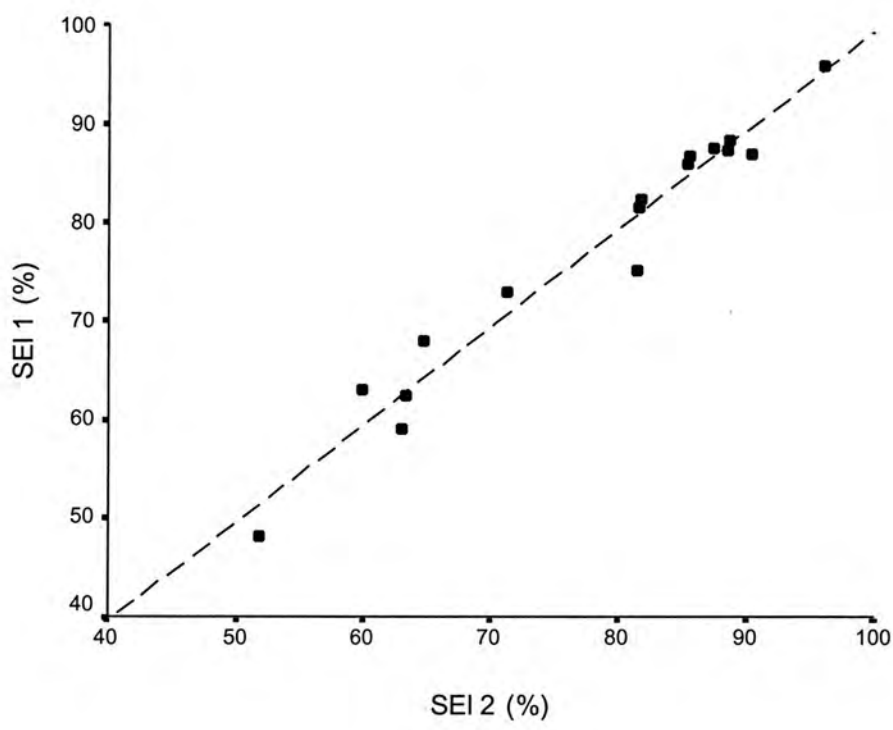


Figure 3.2: Scatterplot of the relationship between first and second arousal index scores for all 16 rescored records

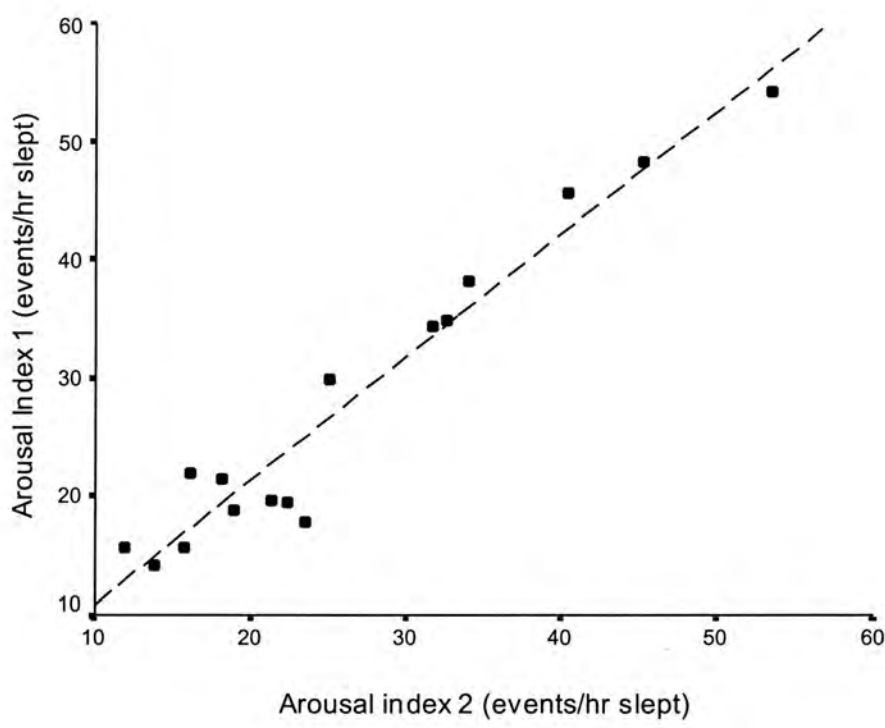




Figure 3.3: Bland Altman plot of the relationship between first and second sleep efficiency index scores for all 16 rescored records

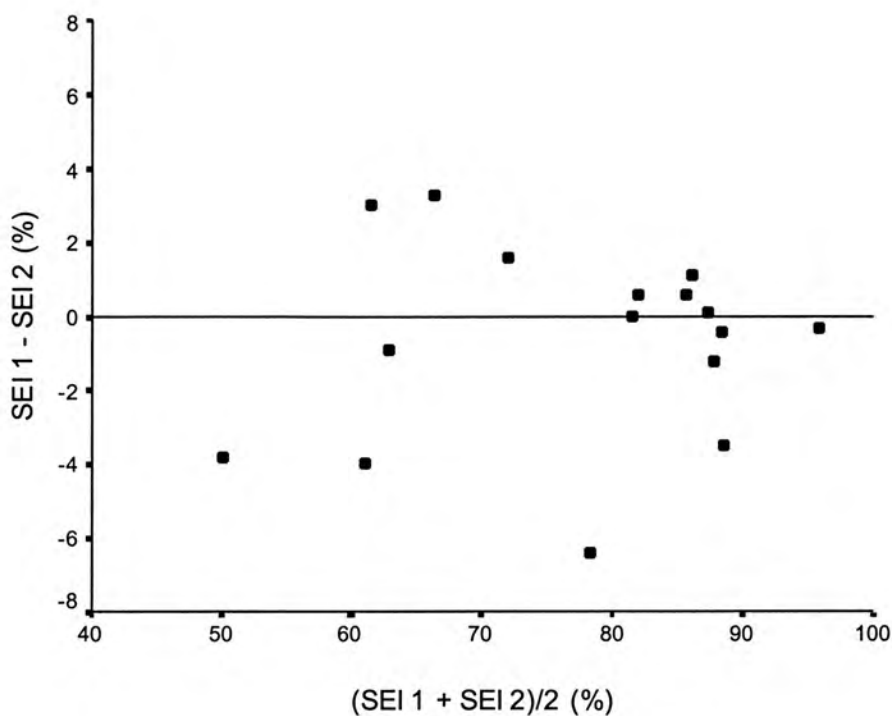
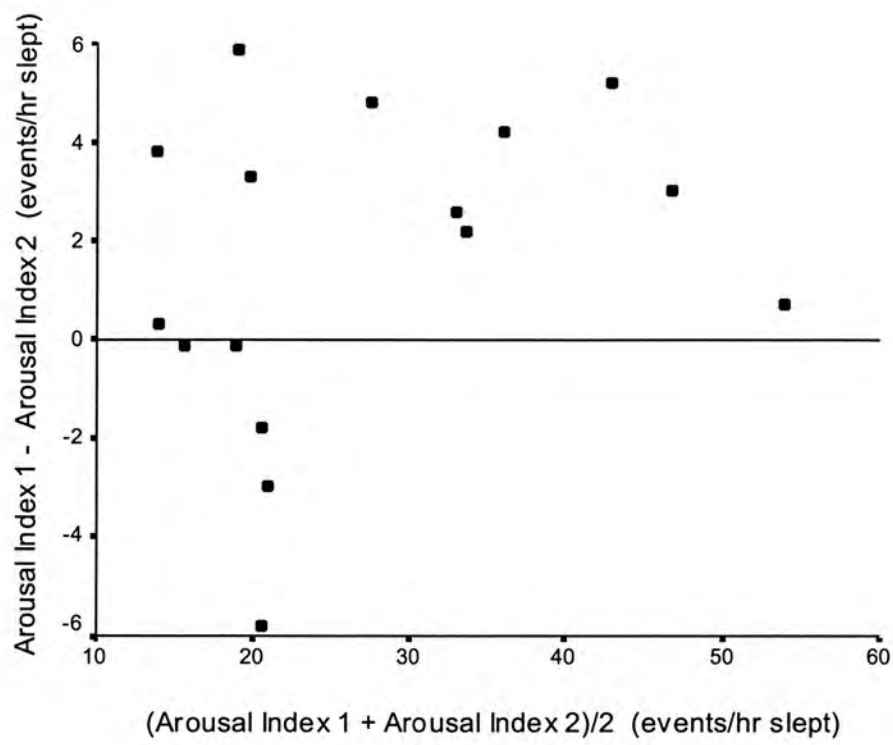


Figure 3.4: Bland Altman plot of the relationship between first and second arousal index scores for all 16 rescored records



### **3.6 Home sleep studies:**

Home PSG monitoring of sleep was done using the Compumedics P-series portable system (Compumedics Sleep Ltd, Abbotsford, Australia). This equipment consists of a number of sensors and electrode channels in a patient interface box, which fits into a cloth vest worn over the nightclothes. The patient interface box connects to a data-acquisition recorder placed by the bedside, which is run by a 15-hour rechargeable battery. The following signals were recorded: Cz-Pz and C3–C4 bipolar EEGs (125 Hz), right and left EOGs, bilateral submental EMGs, and right and left anterior tibial EMGs. Gold electrodes were used to record EEG, EOG, and submental EMGs. Also recorded was “airflow” by a triple oronasal thermistor, chest and abdominal excursions by inductance plethysmography, snoring sounds by tracheal microphone, and oxygen saturation by in-built oximeter with a finger probe.

Portable full PSG sleep recordings in the home can achieve high quality signals and when compared simultaneously with in-laboratory recordings do not differ in measures of objective sleep quality (Fry et al. 1998). We used the same portable sleep recording system as chosen for the Sleep Heart Health Study (SHHS) (Redline et al. 1998b), where the failure rate of obtaining adequate sleep data on unrepeated studies was low (9.4%).

### **3.7 Other assessments:**

#### ***3.7.1 Questionnaire assessments***

##### **Epworth sleepiness scale (ESS)**

The ESS is a widely used, standardized assessment of subjective sleepiness. It asks subjects to rate how likely they are to fall asleep (or doze) in 8 different situations, of differing sleep-inducing potential. Subjects are asked to estimate the likelihood of falling asleep, “in contrast to just feeling tired” in order to distinguish true sleepiness from fatigue. They are also asked how likely this would happen based on their “usual way of life in recent times”, in order to make a general assessment of sleepiness rather than sleepiness at a particular time. For each situation subjects give a score from 0 (not likely to fall asleep) to 3 (highly likely to fall asleep), so that the range of possible scores for the questionnaire is from 0–24. In the original validation study control subjects (n=30) without sleep disorders all had an ESS of  $\leq 10$  and among patients with SAHS the severity of SDB correlated with the ESS (Johns 1991). A larger study, however, found that controls (with normal sleep wake habits and no reported excessive sleepiness) had ESS scores in the range 0-14 (n=188) (Parkes et al. 1998).

### **Functional assessment of sleep questionnaire (FOSQ)**

The FOSQ questionnaire measures the effects of excessive sleepiness on daytime function in a broad range of activities relevant to daily life. The questionnaire has 30 questions covering 5 domains (e.g., vigilance and social outcome) and takes about 15 minutes to complete. It has been shown to have good internal reliability, test-retest reliability, and construct validity (Weaver et al. 1997b).

### **Pittsburgh Sleep Quality Inventory (PSQI)**

The PSQI is a validated questionnaire (Buysse et al. 1989) assessing sleep quality over the previous month. It uses 19 items to assess sleep quality in the following seven different domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. These seven domains can be combined to give a global score. The global score has a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing clinical populations of “good sleepers” (healthy subjects) from “poor sleepers” (depressed and sleep disordered patients) (Buysse et al. 1989).

### **U.K. version of the Short Form 36 quality of life questionnaire (SF 36)**

The SF 36 is a widely used, validated generic quality of life questionnaire. It contains 36 questions, which cover 8 domains reflecting psychological and physical aspects of quality of life. The SF 36 can be used for comparing quality of life among different medical conditions and has been shown to be sensitive to the

effects of sleep disruption due to SAHS (Smith & Shneerson 1995). Two principal components have been derived from these questions. These are the physical and mental component summary scores. U.K. normative values are now available for the summary scores and each of the 8 domains (Jenkinson et al. 1996) and these were used (along with the U.K. version of the questionnaire) in the study reported in chapter 6.

### **The Enrich marital satisfaction questionnaire**

The Enrich (Evaluation and Nurturing Relationship Issues, Communication and Happiness) Marital Satisfaction Scale is a short questionnaire (15 questions) which measures marital adjustment and satisfaction by surveying 10 different domains of marital quality. It contains questions that are used to correct for idealistic distortion (i.e., unrealistically positive descriptions) of marital quality. The results are given as a percentile score based on (U.S.A.) normative values. This questionnaire has been shown to be a reliable and valid tool for measuring marital satisfaction (Fowers & Olson 1993).

### **In-house questionnaires for couples (see appendix b)**

An in-house questionnaire was used to examine the effects of SAHS symptoms and treatment with CPAP on the partners of patients with SAHS. This used a simple 3 or 5-point ordinal scale format, asking participants to assess sleep quality and the severity of sleep disruption (secondary to patient symptoms or CPAP). There were questions about changes in sleep quality and daily functioning with interventions,

and questions about treatment preferences. There were also questions about who decided on the need for medical treatment and main reasons for presenting, as well as the feeling of refreshment in the morning.

### ***3.7.2 Reaction time***

#### **Simple unprepared reaction time (SURT)**

The SURT is a test which measures reaction times to a visual signal presented at random times (Wilkinson & Houghton 1982). A laptop computer, randomly presenting a white block on a black background, was used as a convenient method of testing reaction times in the home. The SURT protocol has been shown to have a very short practice effect before reaching a performance plateau (less than 20 minutes of practice). It is sensitive to sleep disruption. Reaction time variables measured were the median, reciprocal of the reaction times, and the 95<sup>th</sup> percentile of the reaction times. The latter 2 variables have been shown to be particularly sensitive to the effects of sleep deprivation (Dinges & Kribbs 1991). The 95<sup>th</sup> percentile of reaction times is sensitive to performance lapses that occur even with short duration tests (10-20 minutes) that require sustained attention tasks involving a readiness to respond.



## **CHAPTER 4 – LONG-TERM USE OF CPAP THERAPY FOR THE SLEEP APNOEA/HYPOPNOEA SYNDROME**

## **4.1 Introduction:**

As noted in chapter 2.5, CPAP therapy is the treatment of choice for most patients but effectiveness continues only while the treatment is being used. As SAHS is usually a lifelong condition it is extremely important to ensure long-term use of CPAP therapy. There are few studies of objective long-term use of CPAP, with only one (Krieger et al. 1996) involving more than 50 patients with a mean follow-up time of over 1 year. Krieger and colleagues followed 608 patients (including 33 non-apnoeic snorers) on CPAP treatment for a mean of 39 months. In order to clarify the important determinants of long-term compliance with CPAP therapy we followed-up a large group of SAHS patients on whom we have objective data on CPAP use.

## **4.2 Methods:**

### ***4.2.1 Patients studied***

All patients booked for a CPAP titration night between January 1986 and February 1997 at the Scottish National Sleep Center were included. Patients booked for CPAP during this time were managed as outlined in chapter 3.2. A database of the long-term outcomes of all these patients was constructed (chapter 3.3).

### ***4.2.2 Statistical analysis***

Statistical analysis was performed using the STATA Release 4 statistical package (Computing Resource Center, Santa Monica, USA). Non-parametric methods (Mann-

Whitney U, Chi-squared, Spearman rank correlation) were used in the basic descriptive statistical analyses because the variables measured were dichotomous, categorical, or were not normally distributed.

The primary dependent variable of interest was possession and continued use of a CPAP machine. Kaplan-Meier methods of survival analyses were used (Altman 1991), to allow for variable follow-up times. Additionally, the methods of Kaplan-Meier allow the use of 'censored' data; so that all information gathered up until the time of a censored event can be used. 'Censored' events occurred when a patient had died, there was transfer of care, or loss to follow-up. This provides maximum use of available data because continued CPAP use data can be analysed even though the event of interest (deliberate stopping of CPAP treatment) is never reached (Altman 1991).

Univariate analyses (log-rank test) were used to identify explanatory variables influencing continued CPAP use. To explore the independent effects of explanatory variables Cox's proportional hazards model was used (Altman 1991, Cox 1972). The use of Cox's method for survival analysis is analogous to the use of multiple regression as an extension of linear regression. Kaplan-Meier analysis allows the use of both continuous and categorical data. For simplicity and relevance to clinical practice many of the results have been presented using dichotomous data and expressed as hazard ratios.

For all analyses, statistical significance required a two-tailed  $p < 0.05$ . The study had the approval of the local ethics advisory committee.

## **4.3 Results:**

### ***4.3.1 Study population***

In the study period a total of 1,211 patients were booked in for CPAP titration nights and follow-up data were available for 1,155 (95.4%). These data were unavailable in the remaining 56 patients. Comparison of baseline data on the unavailable patients showed that they were not different from the rest of the group in terms of age, BMI, AHI, ESS, or sex (all;  $p > 0.05$ ).

### ***4.3.2 Patients refusing CPAP treatment***

Fifty-two patients (4.5%) were booked for a CPAP titration study but subsequently refused CPAP treatment. These patients either repeatedly failed to attend the titration night ( $n=16$ ) or were unable to tolerate CPAP on the titration night and refused to take CPAP home ( $n=36$ ). When compared with patients who accepted CPAP therapy, patients who refused CPAP were more often female (31% versus 14%,  $p=0.002$ ), current smokers (55% versus 32%,  $p=0.003$ ), or referred by a specialist rather than a family practitioner (80% versus 61%,  $p=0.01$ ). Conversely, these patients were less likely to have a history of witnessed apneas (65% versus 83%,  $p=0.004$ ) and had a lower weekly alcohol consumption (0.5 units versus 6 units,  $p=0.008$ ). Neither severity of sleep disordered breathing, in terms of AHI, nor degree of subjective sleepiness, as measured by the ESS, were significant predictors of CPAP acceptance (table 4.1).

Table 4.1

Baseline data on patients refusing CPAP compared to patients taking CPAP home

Patient characteristics	Patients refusing CPAP*	Patients taking CPAP home*	p value
Number	52	1,103	
Female, %	31	14	0.002
Median age, years	44 (32-57)	50 (43-58)	0.08
Median BMI, kg/m <sup>2</sup>	30 (27-36)	30 (27-35)	>0.1
Median AHI, events/hr slept	22 (13-53)	31 (18-53)	0.07
Median arousal index, events/hr slept	25 (17-43)	32 (20-50)	0.08
Median ESS	12 (6-17)	12 (8-16)	>0.1
Current smoker, %	55	32	0.003
Median alcohol consumption, units/wk	0.5 (0-7)	6 (1-16)	0.008
Hospital referral, %	80	61	0.01
History of snoring, %	100	98	>0.1
History of apnoeas, %	65	83	0.004
History of daytime somnolence, %	84	81	>0.1
History of driving problems, %	48	36	>0.1

\* Values in parentheses are interquartile ranges

#### ***4.3.3 Patients accepting CPAP for home use***

There were 1,103 patients who commenced home CPAP therapy; 86% were male and the median (IQR) age was 50 (43-58) years; BMI 30 (27-35) kg/m<sup>2</sup>; AHI 31 (18-53) events/hr; ESS 12 (8-16). The most common clinical features were a history of snoring (98%), witnessed apneas (83%), and excessive daytime sleepiness (81%). A self-rated ESS >10 was present in 60% of patients and 36% of patients reported difficulties due to sleepiness whilst driving (table 4.1).

Most cases of SAHS were diagnosed with full night polysomnography (933, 80%). The remainder were diagnosed by split-night study (chapter 1.5.2, 3.2.2) (n=45, 4%), EdenTech (n=135, 12%), diagnostic AutoSet (n=23, 2%), or oximetry alone (n=19, 2%). Patients were treated with a median (IQR) CPAP pressure of 8 (7-10) cm H<sub>2</sub>O.

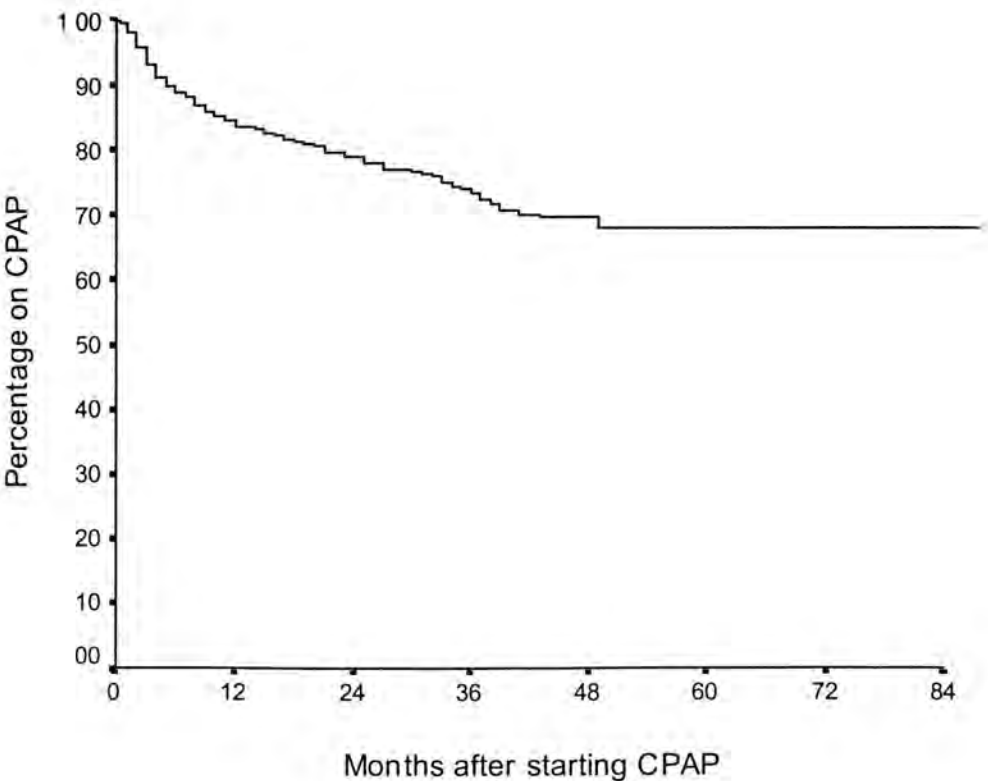
The maximum follow-up duration was 139 months, with 281 patients being followed up for  $\geq 3$  years and 61 for  $\geq 5$  years. The median (IQR) follow-up was 22 (12-36) months, reflecting the exponential rise in referrals over the time of the study. During follow-up 38 patients (3.5%) died (a further 2 patients who refused CPAP are known to have died), another 9 (0.8%) patients had their care transferred to another center and 217 (20%) stopped CPAP. Of the 217 who stopped CPAP, 167 patients (77%) independently decided to stop treatment and 50 (23%) patients had their machine reclaimed by the sleep centre. The reasons for reclamation were due to either persistent use less than 2 hours per night (n=47) or CPAP-induced severe side effects such as recurrent epistaxis (n=3). Reasons why patients stopped using CPAP include lack of benefit (n=112), discomfort (including noise and feelings of claustrophobia) (n=102), and other reasons (cure as a result of weight loss, recurrent epistaxis, alternative diagnosis, and unknown reasons) (n=28). There was more than 1 reason documented in 20 (18%) cases.

The median of the average (IQR) use per night at the most recent clinic visit for all patients who started home CPAP therapy was 5.6 (3.8-7.0) hrs/night and among

patients continuing to use CPAP it was 5.7 (3.9-7.0) hrs/night. In the latter group, 76% of patients used their CPAP machine for an average of at least 3.7 hrs/night.

A Kaplan-Meier plot of the percentage of patients started on CPAP that continue using their machine over time shows that 84% were still using CPAP at 12 months. The use of CPAP seemed to reach a plateau at around 4 years when 68% of patients were still using CPAP (figure 4.1).

Figure 4.1  
Percentage of patients using CPAP versus time





#### ***4.3.4 Determinants of long-term CPAP use***

We sought determinants of long-term CPAP use from baseline data and from median nightly CPAP use at the first clinic follow-up after commencing CPAP therapy (always  $\leq 3$  months). Potential baseline determinants examined were patient-related (age, gender, occupation, and referral source), disease-related [symptoms, ESS, AHI, arousal index, collar-size, BMI, alcohol consumption, smoking status, and co-existing chronic obstructive pulmonary disease (COPD)], and treatment-related (diagnostic study type, method of CPAP titration, and CPAP pressure) variables. This analysis indicated that continued use of CPAP therapy was associated with male sex, lower age, absence of COPD, and increasing values for ESS, AHI, arousal index, BMI, and CPAP pressure. A history of snoring, witnessed apnoeic episodes, daytime somnolence, and problems with somnolence during driving were also associated with continued use of CPAP therapy. Increasing average nightly use of CPAP at the first follow-up visit was associated with long-term CPAP use. The significant variables are shown as dichotomized data (categorized by commonly used clinical cutoffs or by median values) in table 4.2.

Table 4.2

Univariate analysis: variables influencing continued CPAP use

Univariate predictors of continued CPAP use	Hazard ratio*	p value
Women versus men	1.48	0.03
Age $\geq 50$ versus age $< 50$	1.43	0.001
BMI $\leq 30$ versus BMI $> 30$	1.65	0.0003
ESS $\leq 10$ versus ESS $> 10$	1.89	$< 0.0001$
AHI $< 15$ versus AHI $\geq 15$	2.29	$< 0.0001$
AHI $< 30$ versus AHI $\geq 30$	2.26	$< 0.0001$
Nonsnorer versus snorer	2.6	0.006
No apnoeas versus apnoeas	2.25	$< 0.0001$
No somnolence versus somnolence	2.23	$< 0.0001$
No driving problems versus driving problems	2.25	$< 0.0001$
Coexisting COPD versus no COPD	1.6	0.01
CPAP pressure $< 8\text{cmH}_2\text{O}$ versus $\geq 8\text{cmH}_2\text{O}$	1.53	0.002
CPAP usage at 3months $< 2\text{hrs}$ versus $\geq 2\text{hrs}$	12.7	$< 0.0001$

\* Relative risk of stopping CPAP

Cox's proportional hazards models indicated that the independent predictors of long-term CPAP use were a history of snoring ( $p=0.009$ ), AHI  $\geq 15$  ( $p<0.001$ ), and ESS  $> 10$  ( $p<0.001$ ) (table 4.3). Kaplan-Meier plots show role of AHI and the combined role of AHI and ESS on CPAP use at commonly used severity levels (figure 4.2- 4.5). AHI and ESS were independent predictors of continued CPAP use when analysed as continuous variables, predicting use across the range of their values. CPAP use at the first follow-up clinic visit was also a strong independent predictor of continued CPAP use when a separate Cox regression analysis was performed including this additional variable (table 4.3, figure 4.6). Using a cutoff of  $\geq 2$  hours/night at the first visit, the hazard ratio for continuing CPAP is 13.8 (table 4.3).

Figure 4.2

Percentage using CPAP versus time; at 3 AHI levels

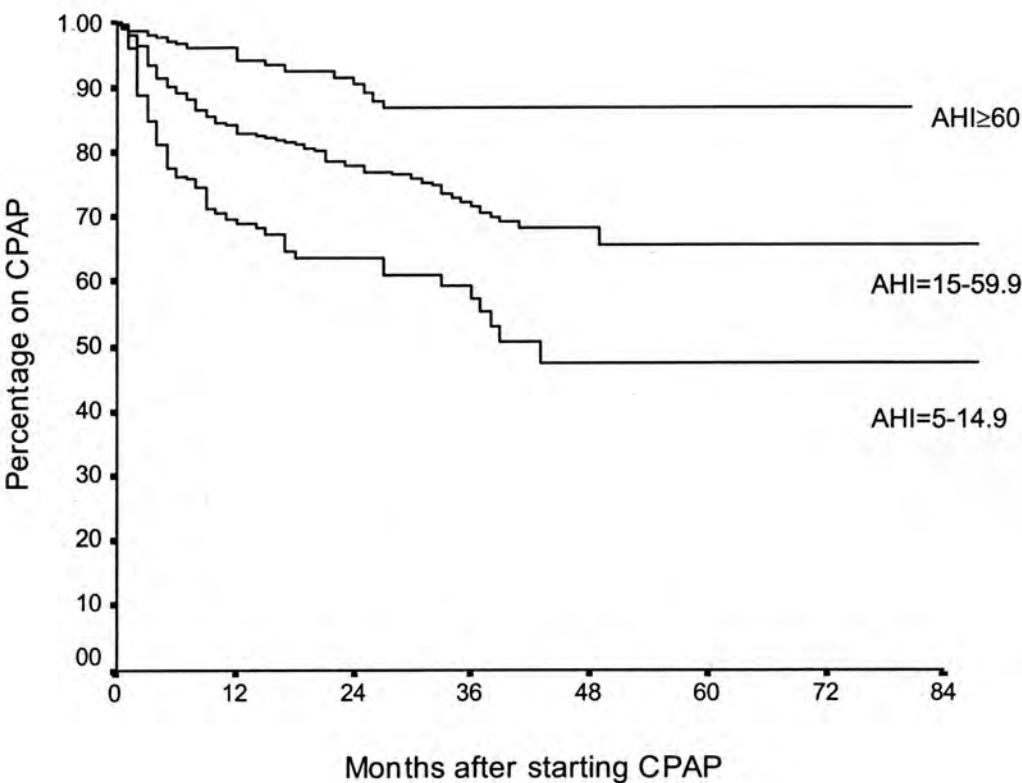


Figure 4.3

Patients with Epworth score  $\leq 10$  at 3 AHI levels: percentage using CPAP versus time

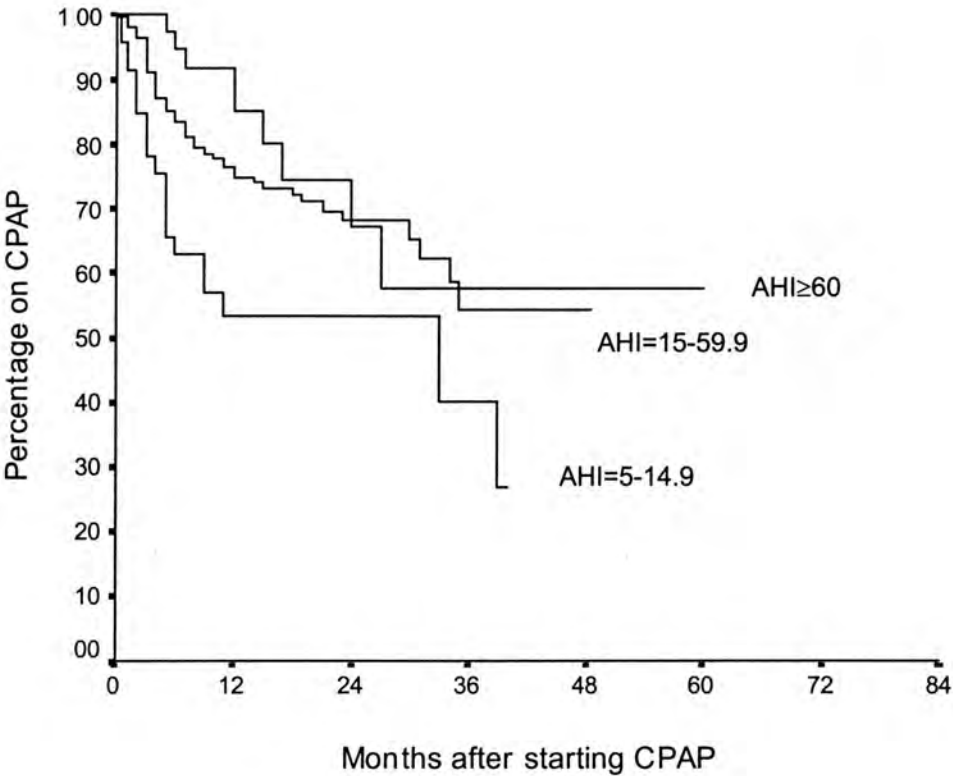


Figure 4.4

Patients with Epworth score 11-15 at 3 AHI levels: percentage using CPAP versus time

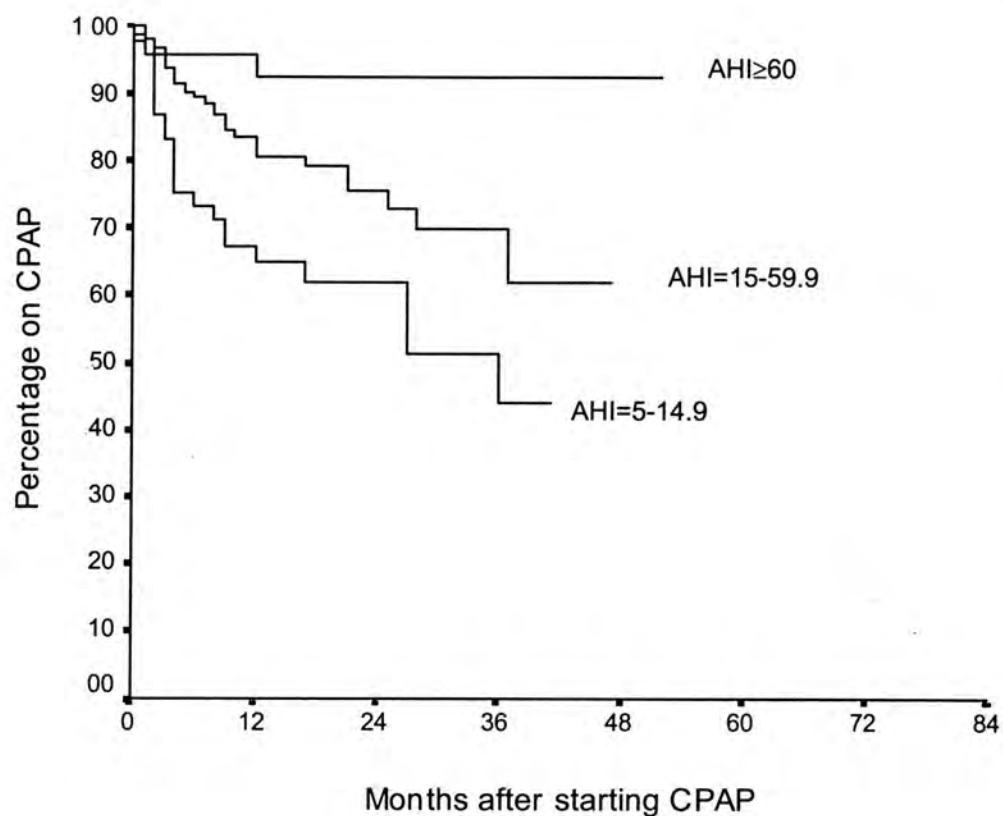


Figure 4.5

Patients with Epworth score  $\geq 16$  at 3 AHI levels: percentage using CPAP versus time

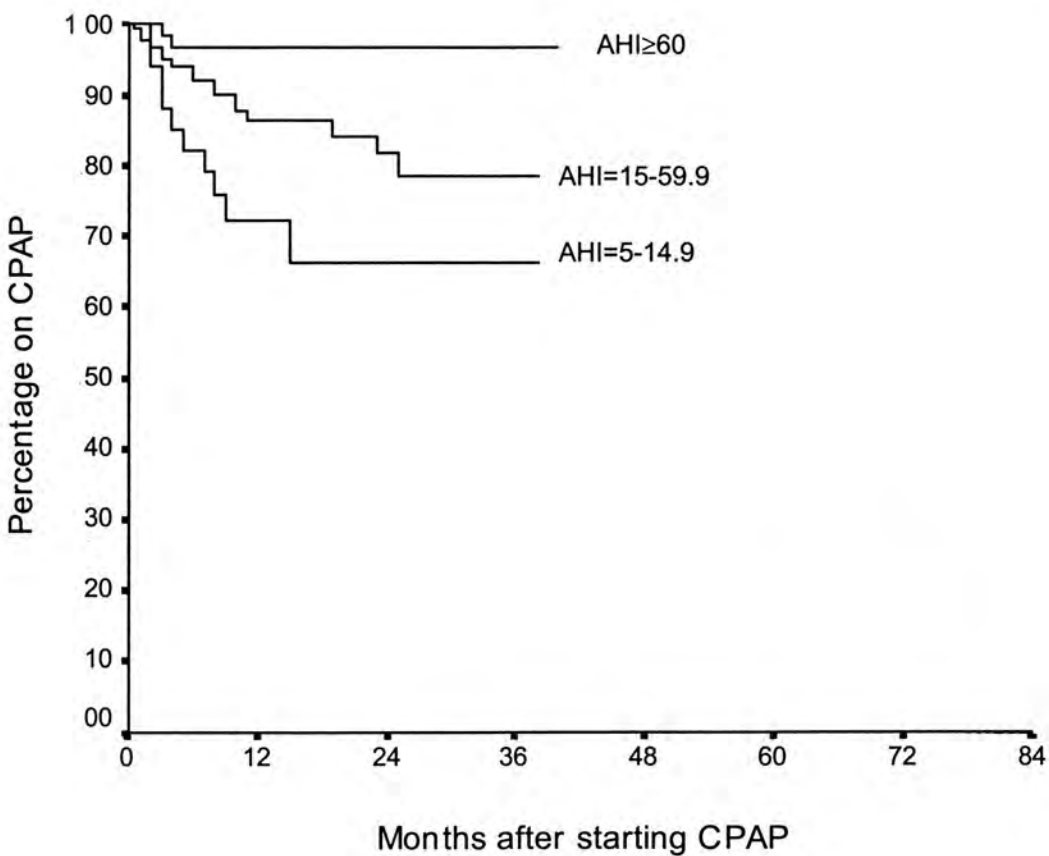


Table 4.3

Multivariate analysis: Independent variables influencing continued CPAP use

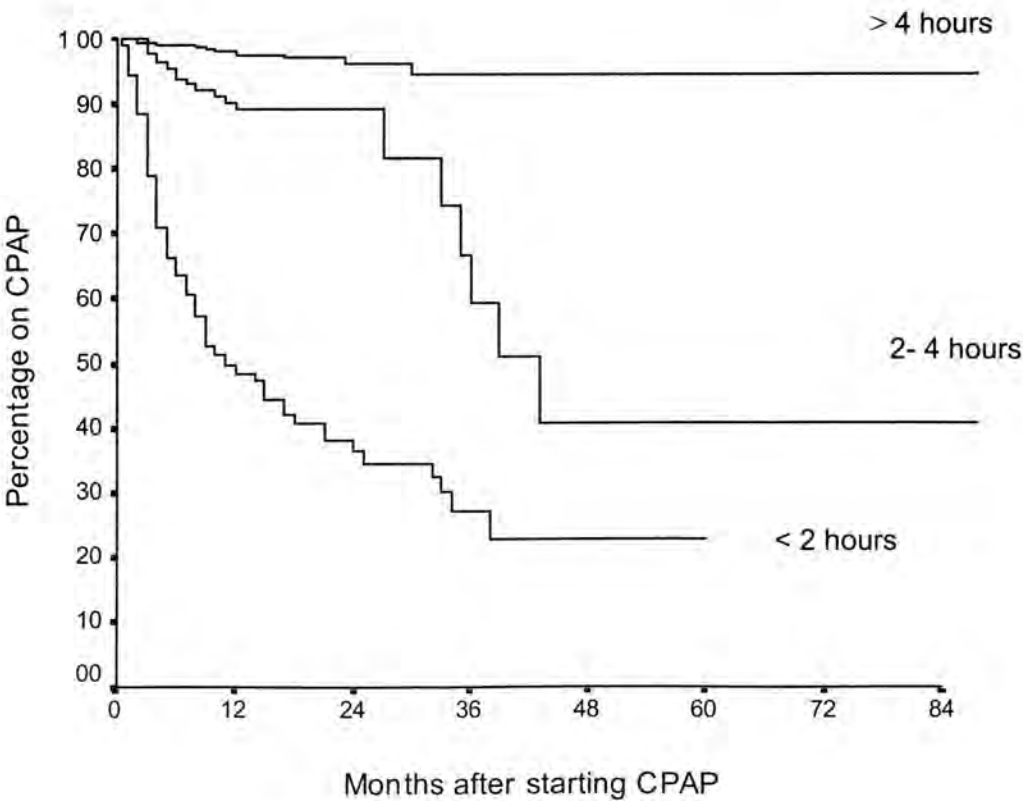
Independent predictors of continued use	Hazard ratio*	95% CI†	p value
AHI <15 versus AHI ≥15	2.48	1.79-3.46	<0.001
ESS ≤10 versus >10	1.92	1.41-2.61	<0.001
Nonsnorer versus snorer	2.76	1.29-5.95	0.009
CPAP use at 3months <2hrs versus ≥2hrs	13.8	8.86-21.5	<0.001

\* Relative risk of stopping CPAP

† 95% confidence interval

Figure 4.6

Percentage using CPAP versus time with varying average nightly run times at the first follow-up clinic visit (always ≤ 3 months)





A number of patients had obstructive sleep apnea and co-existing COPD requiring therapy (n=110, 10%). Of those patients refusing CPAP treatment, 7 (13%) had co-existing COPD and there was no difference in CPAP acceptance rate between COPD and other patients (p=0.3). In the univariate analysis of long-term CPAP use patients with co-existing COPD had a hazard ratio of discontinuing CPAP of 1.6 (p=0.01). The multivariate analysis showed no independent influence from COPD (p>0.2).

Most of the COPD patients had mild-moderate disease and only 8 of those started on CPAP had chronic respiratory failure (defined as a  $\text{PaCO}_2 > 45\text{mmHg}$  and/or a  $\text{PaO}_2 < 60\text{mmHg}$ ). Some of these 8 patients have since been transferred to bilevel positive airway pressure and this has been allowed for by the use of 'censored' variables in our survival analyses. Bilevel treatment has not been analysed in this study.

The significant determinants of the average nightly CPAP use were increasing AHI (p=0.004), BMI (p=0.004), ESS (p=0.046), and age (p=0.03). There was no difference in average nightly CPAP use between those diagnosed by full PSG and those diagnosed by limited sleep studies (p>0.5).

#### **4.4 Discussion:**

In this large follow-up study, with a high rate of ascertainment, we found that continued CPAP use is determined by the severity of subjective sleepiness and the severity of sleep disordered breathing. Continuing CPAP usage at 3 years occurred in

$\geq 70\%$  of those patients with an AHI  $\geq 15$  and an ESS  $>10$ . Previous work from this sleep centre has shown that patients with SAHS and mild SDB (AHI=5–15 events/hr) benefit from treatment over 1 month (Engleman et al. 1997), (Engleman et al. 1999). However, the current study shows that many such patients eventually abandon CPAP, especially if they are not “subjectively” sleepy. Further, long-term use can be predicted most reliably by the average nightly use of the CPAP machine in the first 3 months; those using CPAP  $< 2$  hours per night at 3 months are unlikely to continue with long-term treatment.

Among those taking CPAP home, 68% of patients continued on treatment at 5 years. Patients continued to abandon CPAP over the first 4-5 years of treatment, in contrast to our clinical impression that those who continued using CPAP after the first few months tended to use it long-term. Although patients were less likely to abandon CPAP the longer they had been on it, many ( $n=63$ ; 29%) stopped the treatment after 1 year. Similarly, Krieger and colleagues (Krieger et al. 1996) found that 20% of those who stop treatment do so after 1 year.

In the analysis of continued use the outcome of interest is deliberate stopping of CPAP treatment which includes stopping because the patient abandoned treatment (15.5%) or because the machine was reclaimed for reasons of poor compliance or serious side-effects. CPAP machines were reclaimed on 50 occasions (4.5%). Patients were warned about their poor use with the threat of having their machine reclaimed if use did not improve. This threat led to improved use in some patients whereas others remained unwilling to increase use. The choice of 2 hours as a cutoff

is a somewhat arbitrary value since, as discussed in chapter 2.5.4, there is no known lower limit of average nightly use below which CPAP is ineffective. Different authors have used different criteria of minimal acceptable average nightly use. Kribbs and colleagues (Kribbs et al. 1993b) defined 4 hrs/night as acceptable use and regular use as using 4 hrs/night on at least 70% of nights (i.e., average nightly use =2.8hrs/night). Krieger and colleagues (Krieger et al. 1996) used a 1 hour cutoff (after attempts to improve compliance) for withdrawal of CPAP treatment. We believe that patients consistently using CPAP < 2hrs/night are unlikely to gain benefit even if we had not reclaimed their machines.

A number of smaller studies, some using only subjective reports (Rolfe et al. 1991, Waldhorn et al. 1990) of CPAP use, have attempted to establish the important baseline determinants of long-term CPAP usage with variable results (Rolfe et al. 1991, Waldhorn et al. 1990, Krieger et al. 1996). Our results confirm that the severity of breathing abnormality during sleep (Krieger et al. 1996) and degree of subjective sleepiness (Rolfe et al. 1991, Waldhorn et al. 1990) are predictors of continued CPAP use. Symptoms, sex, age, arousal index, BMI, co-existence of COPD, and CPAP pressure are also relevant factors. As a lack of snoring history was rarely found (2%) amongst our patients this is not a very helpful discriminator in routine clinical practice. The study also shows, for the first time, that AHI and ESS are the independent predictors of long-term CPAP use.

These predictors are relatively weak, as can be seen from their hazard ratios (table 4.3), but they can be combined to give a better prediction (figures 4.3-4.5). Patients who are both very sleepy ( $ESS \geq 16$ ) and have severe disease ( $AHI > 60$  events/hr)

have excellent long-term use of 97% at 3 years (figure 4.5). Sleepy patients with mild-moderate severity disease ( $AHI=15-59.9$  events/hr) also have good long-term use of 79% (figure 4.5). Notably, even very sleepy patients with  $AHI<15$  events/hr have long-term use of 66% (figure 4.5). This suggests that very sleepy patients may be a group who are very susceptible to even borderline increased levels of SDB. In the initial validation study of the Epworth sleepiness scale, all those with an  $ESS\geq 16$  had pathological sleep disorders, and no normal subjects had such increased values of ESS (Johns 1991). This suggests that with high values on the ESS even low levels of SDB should be considered potentially pathologic. Patients with  $ESS=11-15$  showed a similar pattern but had a little lower long-term use than those with  $ESS\geq 16$  (figure 4.4). Patients who are not sleepy ( $ESS<10$ ) and have borderline SDB ( $AHI<15$  events/hr) have poor long-term use, with 40% continuing to use CPAP at 3 years. Non-sleepy patients with higher levels of SDB ( $AHI=15-59.9$  and  $AHI\geq 60$  events/hr) have better, but still sub-optimal, 3 year use of 54-58% (figure 4.3).

There was no significant association between the CPAP pressure and mean nightly CPAP use ( $p=0.09$ ). However, continued CPAP use was greater among patients with higher CPAP pressures. One might expect increased pressure would increase mouth leak and thus nasal symptoms (Richards et al. 1996), possibly worsening compliance. However, physical side effects do not seem to be responsible for poor CPAP compliance (Hoffstein et al. 1992, Kribbs et al. 1993b, Waldhorn et al. 1990). By contrast the 'non-physical' side effect of claustrophobia (Kribbs et al. 1993b), has been associated with worse CPAP use. CPAP pressure was not an

independent predictor of continuing use. Presumably, the relationship between pressure and use resulted from covariance of CPAP pressure with AHI, which was an independent predictor of use. The 95<sup>th</sup> centile of CPAP pressure was 14.2 cm. We are unable to comment with confidence on the effects of pressure on compliance at high pressures (higher than 14 cm).

The main reasons patients stopped treatment were lack of benefit and side effects from CPAP. Although side effects are reported equally in compliant and non-compliant groups (Pepin et al. 1995, Waldhorn et al. 1990, Hoffstein et al. 1992), tolerance of these side effects may differ. Evidence for this view comes from Pepin and colleagues (Pepin et al. 1995), who found that CPAP was considered to be noisier by patients with mild compared to more severe SAHS. It is probable that the balance of benefits to side effects is important in determining continued CPAP use.

In contrast to baseline information, average nightly CPAP use within 3 months of starting CPAP is strongly predictive of long-term use. Our findings extend those of Kribbs and colleagues (Kribbs et al. 1993b) who found that the pattern of CPAP use during the first 3 months is usually established in the first month, and possibly as early as the first 4 days (Weaver et al. 1997a). Although early average nightly use data is predictive as a continuous variable, an arbitrary cutoff of 2 hrs/night will separate most long-term CPAP users from those who stop. The likelihood of stopping CPAP is much higher if CPAP use is less than 2 hrs/night in the first 3 months, with only 22% continuing long-term use (figure 4.6), compared with 78% for the remaining patients. The importance of early use data in predicting continuing CPAP use may mean that there is a window of opportunity, shortly after



starting CPAP, to influence future compliance. Increased patient education and support may be effective in achieving this, as discussed in chapter 2.3.2. There may, however, be a number of patients who are unable to tolerate CPAP treatment and who will not continue using CPAP long-term. Early identification of these patients would be useful so that resources could be deployed elsewhere and alternative treatments tried instead.

Only 4.5% of patients in this sleep centre refused CPAP treatment, less than the 15-50% reported by other investigators (Krieger et al. 1996, Rauscher et al. 1991a, Waldhorn et al. 1990). As described in chapter 3.2.2, patients in this centre receive comprehensive pre-CPAP education. Because others (Waldhorn et al. 1990, Krieger et al. 1996) reported unknown or limited pre-treatment education, it is postulated that the education provided by our centre may be a reason for the high acceptance of CPAP. Free CPAP provision could also be a factor in initial acceptance but Rauscher and colleagues offered CPAP free to unselected patients with AHI > 15 with an acceptance rate of only 50% (Rauscher et al. 1991a). Thus patient selection may be another important factor as all our patients had to be symptomatic - with either significant sleepiness or 2 other major features of SAHS - to be offered CPAP. In the current study and another (Waldhorn et al. 1990), some patients may have been advised to begin CPAP treatment in the clinic but refused without therefore being booked for CPAP titration. The exact number of these patients remains unknown in this study, however either NJD or TM directly made the decision to offer CPAP in all patients and this number was very small (estimate <10 patients).

Of those refusing CPAP treatment a disproportionate number were female, which has not been reported by others (Krieger et al. 1996, Rauscher et al. 1991a, Waldhorn et al. 1990). Witnessed apnoeas may provoke a degree of anxiety among patients so that they persevere at least beyond a CPAP titration night. The finding that CPAP refusers were more often specialist-referred is probably because 38% of such patients were referred from ENT specialists and many of these presented with snoring as the main complaint. Presumably, many of these patients had a partner-requested referral and will be less concerned about their own symptoms, perhaps decreasing motivation for therapy (Rolfe et al. 1991, Hoy et al. 1999). CPAP refusers also drank less alcohol and were more often current smokers, but the reasons for these relationships are unclear.

The median nightly use of CPAP determined from clocks built into the machine was 5.7 hours in those who continued with CPAP therapy. No lower threshold for effectiveness of CPAP is known. However, Engleman and colleagues were able to show improvements in objective daytime sleepiness, symptom scores, mood, and cognitive function in a group of consecutive SAHS patients with an average CPAP use of 3.7 hours per night (Engleman et al. 1994a). Seventy-six percent of our patients used their CPAP machine for an average of  $\geq 3.7$  per night. The rates of use quoted above refer to time the machine is running, not time at the pre-set therapeutic pressure, however, as discussed in chapter 2.5.3, a correction factor of 0.9 will give a reasonable estimation of time at therapeutic mask pressure. Also, as discussed in chapter 2.5.4, average nightly CPAP use figures do not indicate whether use has been regular or irregular.

One hundred and six patients had CPAP titration with an intelligent device (using AutoSet). All of the remaining patients (n=1105) had, or were booked to have, manual CPAP titrations. These 2 groups of patients were both predominantly male and similar in terms of median age (AutoSet=50 years, manual=50 years,  $p=0.4$ ), BMI (AutoSet=30 kg/m<sup>2</sup>, manual=30 kg/m<sup>2</sup>,  $p=0.8$ ), AHI (AutoSet=32 events/hr, manual=31 events/hr,  $p=0.08$ ), and ESS (AutoSet=13, manual=12,  $p=0.7$ ). Two of the patients receiving Autoset CPAP titration refused to take CPAP home. Kaplan-Meier survival plots of continued use were similar (log-rank test,  $p=0.11$ ). Thus, the patients titrated using AutoSet were similar to those titrated manually and had similar long-term compliance and are therefore included in the analysis.

One of the potential criticisms of this study is that it involved 46 comparisons. By chance alone, two or three relationships would be expected to be significant at the 0.05 level, whereas 23 significant relationships were found. There is no universally accepted statistical solution to this problem and most statisticians feel that Bonferroni correction for multiple comparisons is an overly conservative approach for such correlational analysis of independently acquired data. However, even with a Bonferroni correction, there are still significant univariate relations between continued CPAP use and age, BMI, ESS, AHI, symptoms of SAHS, and CPAP pressure. With Bonferroni correction the independent determinants of continued CPAP use are AHI and ESS (snoring history is no longer significant).

This study was conducted in a health care system where there was no treatment cost for the patient. Although cost is a potential determinant of compliance in systems



where treatment is not free the available evidence suggests that it may not be an important factor in continued CPAP use. Studies in cost-free systems of subjective continued use (Hoffstein et al. 1992), and objective short-term use (Engleman et al. 1994b), had similar levels of use to that in the United States (Kribbs et al. 1993b), arguing against a significant effect of cost. Further, Rolfe and colleagues assessed reasons for discontinuing CPAP treatment in Australia where patients were asked to buy their CPAP machine, and cost was not commonly given as a reason for discontinuing CPAP treatment (6 of 61 patients discontinuing) (Rolfe et al. 1991). It is, therefore, likely that the most of the findings of this study are also applicable to health systems that involve costs to the patient for CPAP treatment.

The effects of a strongly supportive system on long-term use are uncertain. Waldhorn (Waldhorn et al. 1990) reported on subjective CPAP compliance in a system with limited follow-up support ("A follow-up home visit was provided by a respiratory care company on initiation of home therapy"). They found 76% of patients starting CPAP were still using it at an average of 14 months, comparable to the 82% in our center at 14 months. Hence, our findings on long-term use of CPAP may apply to centers with a less supportive system than our own.

A limitation of this study includes the failure to follow-up 4.6% of patients. However, we believe that selection bias has been minimized by the availability of data from nearly all patients in the study group. Furthermore, the remaining patients were similar to the study group in important baseline determinants of CPAP use. All the objective data used in the study were accrued prospectively thus avoiding potential bias from retrospective evaluation of data.

Other limitations include the facts that the ESS has only been in use since 1991 (Johns 1991) and objective data from in-built clocks were not available in the early years of the study (pre-1990). However, all patients were subsequently changed over to CPAP machines with in-built time clocks; there are only 5 patients who started CPAP before 1990 and then stopped before being changed to machines with built-in time clocks. We, therefore, have objective compliance data on the vast majority of patients starting CPAP before 1990. In addition, as we only successfully followed 281 patients at 3 years and 61 patients beyond 5 years, longer-term studies will be required in the future.

#### **4.5 Conclusions:**

In conclusion, this study found that in a cost free system, with comprehensive pre-CPAP education very few symptomatic patients refused CPAP treatment and they were more often women, were more often specialist-referred, and less often had a history of witnessed apnoeas. Just over two thirds of patients who took CPAP home continued with CPAP at 5 years, with a median nightly use of 5.7 hours. Although AHI, subjective daytime sleepiness, and snoring history have an independent role in predicting long-term CPAP use they are weak predictors and should not be used in isolation to determine who merits a trial of CPAP treatment. Early CPAP use data are strongly predictive of continuing use and may help decisions about perseverance with CPAP treatment and allow early identification of patients who might benefit from more intensive education and support (Hoy et al. 1999). It also suggests that efforts to improve CPAP compliance should be targeted to the initial 3 months.

**CHAPTER 5 - SPLIT-NIGHT SLEEP STUDIES**

## **5.1 Introduction:**

Many sleep centres are struggling to cope with the number of patients being referred and the financial burden of investigating and treating them. In many centres waiting times from referral to treatment is long, often > 1 year. One way to reduce the time taken to investigate and treat patients is to use split-night studies. This means that a diagnostic PSG and a CPAP titration are done on the same night, rather than the standard 2 nights consisting of a diagnostic PSG night and subsequent CPAP titration night (full night patients) (chapter 1.5.2, 3.2.2). Despite the potential savings, split-night studies are not widely used in all countries, at least partly because of concerns about the unknown long-term outcome of these studies (Jamieson 1991). Some studies that have included clinically relevant outcomes have not used a control group (Fleury et al. 1994). When a control group the only outcome measured was average nightly CPAP use at the first follow-up clinic visit (Strollo et al. 1996, Sanders et al. 2000). We have, therefore, performed a larger scale study of the effectiveness of split-night studies.

## **5.2 Methods:**

### ***5.2.1 Matching criteria***

We used our database of patients booked for CPAP titration between 1986 and 1997, described in chapter 3.3, and undertook a matched controlled comparison using prospectively gathered data on CPAP use and patient outcomes. Every patient who had a split-night study was matched with 2 patients who had undergone full

night diagnostic and CPAP titration studies. Matching of split-night studies with full night studies was performed using the AHI and the ESS, blind to study outcomes. These variables were chosen as they were found to be the independent predictors of long-term CPAP use in our previous study on this group of patients (chapter 4). All patients booked for a split-night study during the study period were included providing that they had been given a pre-treatment ESS [ESS was not in use prior to 1991 (Johns 1991)].

All full night patients were matched to the split-night patients for the 2 criteria:

1. AHI within 15%
2. ESS within 3 units

### ***5.2.2 Inclusion/exclusion criteria***

Patients were evaluated for the symptoms and signs of SAHS (Whyte et al. 1989) by a physician experienced in sleep medicine. Split-night studies were performed after clinical evaluation if there were:

- (1) Clinical features 'classical' of SAHS; this required the presence of loud snoring, witnessed apnoeas, and an unequivocal history of excessive daytime somnolence (including an ESS > 10).
- (2) A good history of SAHS and a supportive investigation from another centre.

A supportive investigation included:

Suggestive overnight oximetry or a limited channel study (without EEG recording) with an apnoea/hypopnoea rate/hr recorded of >5 but <30 (chapter 3.2.1).

or

(3) A good history of SAHS and logistical reasons (e.g., a long distance to travel for investigation).

If there were symptoms suggestive of other sleep disorders, such as narcolepsy, patients were not booked for split-night studies. During the diagnostic portion of the split-night study the specialist night nurse estimated the AHI, after 2-3 hours of sleep. If the night nurse thought the AHI in the diagnostic portion of the study was  $> 20$  events/hr, manual CPAP titration was then undertaken. Formal scoring of the AHI in the split-night patients was not performed during the night, but was left until the following day. Full night patients were booked for CPAP titration because there were 2 or more major symptoms of SAHS (Whyte et al. 1989) and an AHI  $> 5$  events/hr slept. Polysomnography was performed with our usual equipment and scoring techniques (chapter 3.2.1, 3.4).

All patients received standard education (chapter 3.2.2) before a CPAP titration night or a split-night study. Patients booked for a split-night study were told that CPAP treatment was likely to be needed and, if so, would be initiated during the night. When CPAP treatment was started on a split-night study the CPAP mask was placed over the existing monitoring leads in order to minimise patient disturbance.

### ***5.2.3 Outcomes measured***

At clinic follow up, patients completed an ESS questionnaire and the average nightly CPAP use was calculated from the time clock reading. Details of nursing

interventions were obtained from the specialist CPAP nurses' records and the clinical records. They were classified into 8 categories: mask changes, pressure changes, topical nasal steroids/nasal ipratropium/other nasal topical, provision of humidifiers, telephone advice, and "other" interventions. The total of all nursing interventions for each patient was also calculated. The median frequency of nursing interventions in each group was calculated using the number of nursing interventions as the numerator and the follow-up time as the denominator for each subject. A similar calculation was made for the frequency of clinic visits. The median time from referral to CPAP treatment was also calculated for each group.

Split-night patients were further classified according to whether the oxygen saturation trace, during the diagnostic portion of the assessment, was considered to be definite for SAHS i.e., showed repetitive dipping of oxygen levels on visual inspection (Douglas et al. 1992).

#### ***5.2.4 Statistical analysis***

Statistical analysis was performed using the SPSS statistical software package (SPSS Inc., Chicago, IL, USA). Non-parametric methods were used (Mann-Whitney U test, Chi-squared test, and Spearman rank correlation) because the variables measured were dichotomous, categorical, or not normally distributed. To analyse the effects of independent variables on long-term CPAP use the methods of Kaplan-Meier survival analysis were used (Altman 1991). The log-rank test was used to compare the effect of dichotomous variables (e.g., study type: split-night versus full night studies) on long-term CPAP use. To further evaluate the role of



possible explanatory variables on long-term CPAP use in the split-night group, the Cox's proportional hazard's model (Altman 1991, Cox 1972) was used. Further details of the rationale behind the methods of Kaplan-Meier are in chapter 4.2.2. For all analyses, statistical significance required a two-tailed  $p < 0.05$ .

### **5.3 Results:**

#### ***5.3.1 Patients studied***

Between 1991 and 1997, a total of 49 patients were booked for a split-night study. Of these, 1 patient failed to attend for the split-night study, 1 refused to take the CPAP machine home after the study, and 1 did not require CPAP treatment after the split-night study was converted to a full diagnostic night. The remaining 46 split-night patients were matched with 92 full night patients, making a total of 138 subjects evaluated for long-term outcomes.

Patients underwent a split-night study because of a classical history of SAHS (n=27), a good history of SAHS and supportive limited investigation (n=13), or for logistical reasons (n=6) (table 5.1).



Table 5.1

Reasons for split-night study

Reason	Number of patients	Percentage of patients	median AHI (IQR*)
Classical history	27	59%	80 (20-126)
Good history and supportive investigation	13	28%	40 (22-64)
Logistical	6	13%	17 (11-48)

\* IQR = interquartile range

Baseline comparisons of split-night patients with control patients showed they were well matched in terms of AHI, ESS, BMI, age, sex, proportion of patients with classical symptoms of SAHS, and CPAP titration pressure (table 5.2).

Table 5.2

Baseline comparison of split-night and full night patients

Baseline patient characteristics	Split-night patients* (n= 46)	full night patients* (n=92)	p value
Male, %	80	83	0.9
Median age, years	50 (42-56)	49 (43-56)	0.6
Median BMI, kg/m <sup>2</sup>	34 (27-42)	32 (28-39)	0.4
Median ESS	15 (10-19)	15 (9-18)	0.7
Median AHI, events/hr slept	49 (18-98)	49 (18-103)	0.9
Proportion classical symptoms	27/46	52/92	0.8
Median CPAP pressure, cm H <sub>2</sub> O	8.5 (7.6-12)	9.0 (7.5-12)	0.9

\* Values in parentheses are interquartile ranges

### 5.3.2 Comparisons of outcomes for all patients

In the diagnostic phase the TST, TRT, stage 1, stage 2, stage 3+4, and stage REM time were all shorter for the split-night group compared to the full night group (table 5.3). However, the SEI was the same for both groups (table 5.3). The TRT during CPAP titration was longer in the full night group but the titration AHI (at the final titration pressure) was similar in the two groups (table 5.3).

Table 5.3

Comparison of polysomnographic results of split-night with full night patients

Polysomnographic variables	Split-night patients*	full night patients*	p value
Median diagnostic TRT, min	131 (116-170)	462 (422-481)	<0.0001
Median diagnostic TST, min	104 (68-134)	322 (229-386)	<0.0001
Diagnostic stage 1, min	6 (2-12)	24 (10-52)	<0.0001
Diagnostic stage 2, min	66(41-86)	170 (120-235)	<0.0001
Diagnostic stage 3 & 4, min	20 (0-33)	34 (8-66)	0.0005
Diagnostic stage REM, min	13 (0-21)	49 (31-73)	<0.0001
Diagnostic SEI, %	74 (57-83)	74 (58-83)	0.8
CPAP TRT, min	340 (300-354)	466 (438-485)	<0.0001
Median titration AHI, events/hr	9 (4-14)	5 (2-13)	0.1

Abbreviations: TRT=total recording time, TST=total sleep time, SEI=sleep efficiency index, \* Values in parentheses are interquartile ranges

Split-night patients were followed up for a median of 22 months and full night patients for a median of 27 months. During this time 10/46 patients (22%) in the split-night group stopped CPAP treatment and a similar proportion of the full night

group [19/92 patients, (21%)] stopped. One patient in the full night group died. Patients who had split-night studies stopped CPAP because of discomfort (n=6) or because of lack of benefit (n=4). Patients in the full night group stopped because of lack of benefit (n=12), discomfort (n=8), and/or other reasons (n=1) (more than one reason was given by some patients). There was no difference between the groups in continued CPAP use (fig 5.1, log-rank test, p=0.6) or in average nightly CPAP use among those continuing to use CPAP (table 5.4).

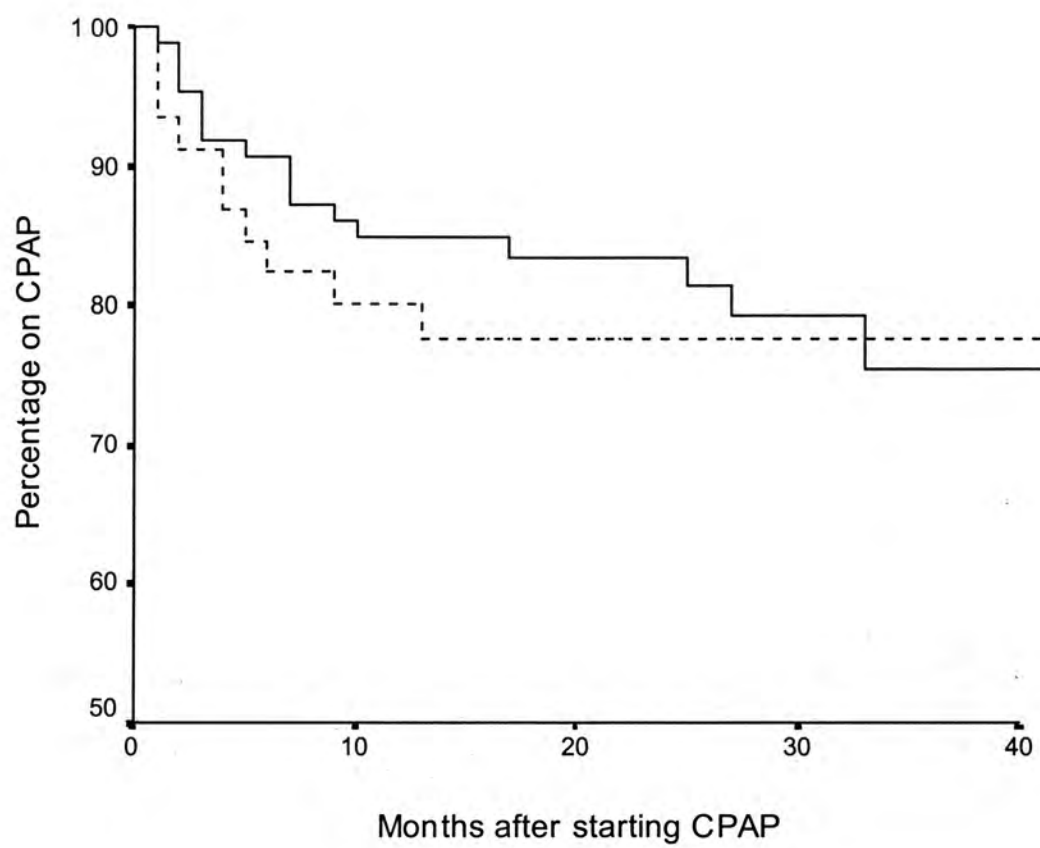
The frequency of nursing interventions and clinic visits needed was similar in the 2 groups (table 5.4). Analysis of each of the 8 categories of nursing interventions did not reveal any differences between the groups in any category of intervention. The post-treatment ESS on patients who continued to use CPAP treatment was similar in each group (table 5.4). The median (IQR) time from referral to starting CPAP treatment was less for the split-night patients than for the full night patients [split-night = 13 (10-20) months, full night = 22 (11-34) months, p=0.003].

TABLE 5.4: Comparison of outcome measures of split-night with full night patients

Outcomes	Split-night patients*	full night patients*	p value
Median nightly CPAP use, hr/night	6.0 (3.8-7.4)	6.2 (3.7-7.0)	0.9
Frequency nursing interventions, number/year	1.0 (0-2.6)	0.8 (0.3-2.4)	0.9
Frequency clinic visits, number/year	2.3 (1.7-2.9)	2.0 (1.4-2.7)	0.1
ESS - patients on CPAP	7 (3-12)	9 (4-13)	0.3

\* Values in parentheses are interquartile ranges

Figure 5.1 Long-term CPAP use: split-night versus full night



Legend: — full night (n=92), - - - split-night (n=46)

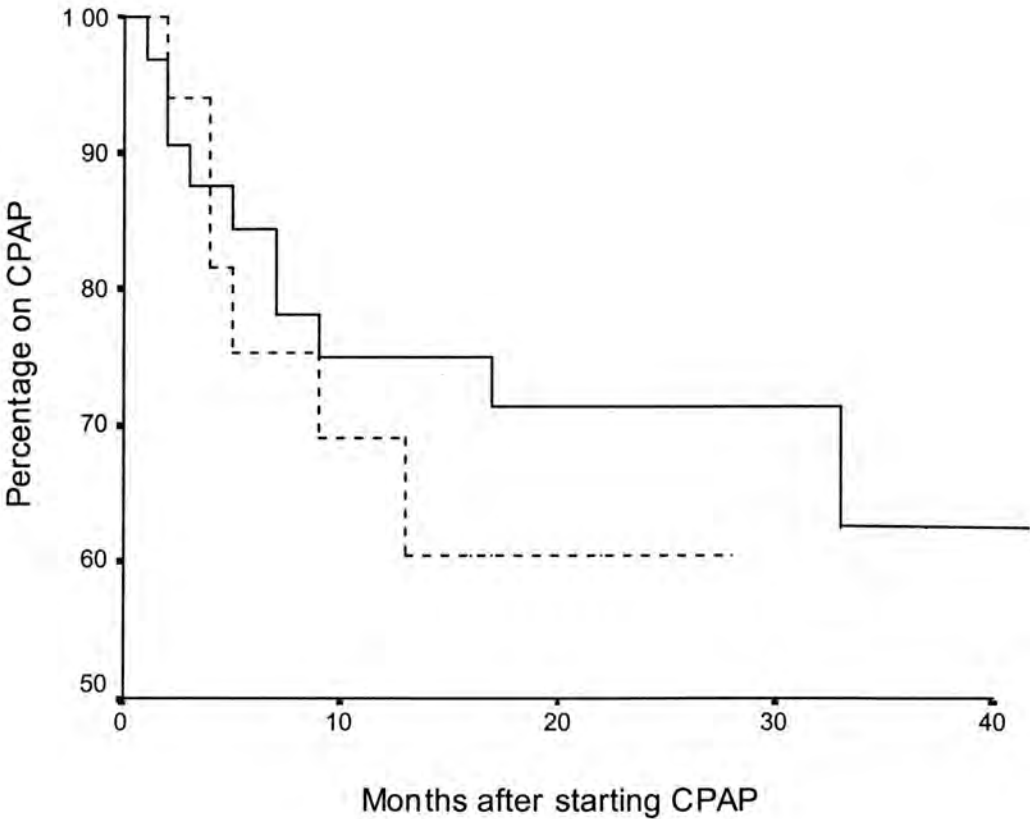
### ***5.3.3 CPAP use in subgroups of patients***

Five of the 46 patients in the split-night group required a further night in the sleep centre. Two had their split-night study converted to a full diagnostic study as the nurse performing the study estimated the AHI as <20 events/hr. These were shown on all night PSG to have AHIs of 12 and 13 events/hr and subsequently underwent a full CPAP titration night for mild severity disease. Three required a second night of CPAP titration, because they were unable to tolerate the split-night CPAP titration. The same proportion of full night patients needed two CPAP titration nights (6/92). Analysis of all outcome measures, using only those 41 split-night patients that did not require a further CPAP titration night (and their matched controls) did not alter any of the findings.

The effect of CPAP titration with and without a REM period at the final pressure on CPAP use was evaluated in those 41 patients whose CPAP pressure was determined from the split-night titration. Patients who had REM, at final pressure, during the titration study (n=33) were similar to those that did not have REM (n=8) in their median (IQR) AHI [REM 64 (19-111) events/hr, No REM 31 (22-123) events/hr,  $p=0.9$ ] and ESS [REM 15 (10-17.5), No REM 17 (6-20),  $p=0.7$ ]. There was no difference in continued CPAP use whether there was a REM period during the titration or not (log-rank test,  $p=0.3$ ). Additionally, there was no difference in median (IQR) nightly CPAP use between these groups [REM 6.5 (4.2-7.7) hr/night, No REM 5.3 (2.8-6.7) hr/night,  $p=0.4$ ].

Continued CPAP use in the sub-group with mild severity SDB, which we define as  $AHI \leq 30$ , was similar in split-night ( $n=17$ ) and full night ( $n=34$ ) patients (log-rank test,  $p=0.5$ ) (fig 5.2). The median (IQR) nightly CPAP use for the mild patients who continued using CPAP was similar [split-night 6.7 (3.9-7.2) hr/night, full night 6.2 (4.6-6.8) hr/night,  $p=0.5$ ].

Figure 5.2 Long-term CPAP use; Mild disease:  $AHI \leq 30$



Legend: — full night (n=34), - - - split-night (n=17)

Cox's proportional hazards model showed that the independent determinants of continued CPAP use in the split-night patients were increasing pre-treatment ESS and decreasing TST of the diagnostic half of the study. Patients with a typical pattern of oxygen desaturation (n=21) had a shorter diagnostic median (IQR) TST than those without a typical pattern of desaturation (n=20) [typical desaturation 82 (57-112) min, not typical 113 (101-140) min (p=0.002)].

#### **5.4 Discussion:**

This study shows that in selected patients, mostly with classical symptoms of SAHS, a split-night study resulted in similar CPAP use and post-treatment ESS to standard full nights of diagnostic PSG and CPAP titration. The frequency of follow-up nursing interventions and clinic visits was the same for both groups but importantly split-night patients had a shorter waiting time from referral to CPAP treatment. Patients with mild severity disease ( $AHI \leq 30$ ) had similar CPAP use in the split-night and full night groups. The absence of REM during CPAP pressure titration (at final pressure) was not associated with lower CPAP use. The reduction in the number of overnight admissions to the sleep centre, without any increase in follow-up intervention, suggests that the split-night protocol may result in significant cost savings.

There have been few reported assessments of outcomes of split-night studies. Fleury and colleagues (Fleury et al.) evaluated 31 patients booked for split-night studies, with a mean CPAP nightly use of 6.7 hours among those continuing to use CPAP



(n=17). It was concluded that patients undergoing split-night studies had similar CPAP use to those having full night studies; however, this conclusion was based on uncontrolled historical comparisons with full night studies. The split-night technique was believed to be reliable and cost saving but no other assessment of effectiveness was made and there were no measurements of interventions needed. Fleury and colleagues found continued CPAP use among those taking CPAP home was 80%, after a mean follow-up time of 9.5 months (Fleury et al. 1994). The current study also found 80% of patients were using CPAP at 9.5 months and that 78% were still using CPAP at 22 months. Strollo and colleagues (Strollo et al. 1996) performed a retrospective, matched (age, sex, and severity of obstructive breathing) controlled comparison of average nightly CPAP use 4-6 weeks after starting CPAP in split-night and full night patients. There were no other outcomes measured. No difference was found between the groups in CPAP use, however the number of patients studied was small (12 in each group) and a type 2 error cannot be excluded. A recently reported study, by the same group using the same design but with more patients, found no difference between split-night (n=18 on CPAP, 6 bilevel pressure) and full night (n=24) groups in average nightly use at 6 weeks (Sanders et al. 2000). We have addressed some of the shortcomings of the above studies by examining a larger group of consecutive patients with follow-up times of around 2 years. We have also included other relevant assessments such as follow-up ESS and the frequency of nursing and medical interventions needed.

In the current study the split-night CPAP refusal rate ( $2/49 = 4\%$ ) was similar to our refusal rate for all patients booked for CPAP between 1986 and 1997 (4.5%) (chapter 4.3.2). Our refusal percentage of 4% was considerably lower than split-



night refusal rates reported by others (16-37.5%) (Fleury et al. 1994 149, Strollo et al. 1996, Sanders et al. 2000). The reason for our better acceptance rate is uncertain but may relate to the use of extensive education before all split-night studies. This education is similar to that used before CPAP titration nights for full night patients (outlined in chapter 3.2.2). By contrast, Fleury and colleagues (Fleury et al. 1994) did not report the use of education prior to split-night studies and Strollo and colleagues (Strollo et al. 1996) reported only that patients were allowed to try a variety of commercially available masks before the study.

The proportion of patients requiring an additional CPAP titration night was the similar in the split-night and full night groups. There has been concern that the shorter time spent interacting with sleep centre staff in split-night studies could adversely influence CPAP use (Jamieson 1991). Therefore, a separate analysis of outcomes was performed, excluding split-night patients that had an extra CPAP titration night. This did not change any of the findings. Additionally, two patients in the split-night group had a sub-optimal CPAP titration; with AHI's of 60 and 70 events/hr slept at the end of their CPAP titration studies. However, these patients had severe disease (baseline AHI = 195 and 180 events/hr slept, ESS = 17 and 13, respectively) and were keen to take CPAP home. They were managed without a further CPAP titration night and their follow-up ESSs were 5 and 9, respectively. Combining these patients with those that required a further full night of CPAP titration gave an "unsuccessful" split-night titration rate of 7/46 (15%), which is similar to previously reported figures of 13% (Fleury et al. 1994) and 15% (Strollo et al. 1996).

Stage REM sleep is associated with more severe disturbances of upper airway function (Charbonneau et al. 1994). It has been suggested that adequate split-night studies should include REM sleep during CPAP titration at final CPAP pressure (Strollo et al. 1996). Among the split-night patients who did not need a second CPAP titration night, those with REM at final titration pressure were compared to those without REM. These groups were of similar severity in baseline AHI and ESS and also had similar CPAP use. This suggests that the presence of REM sleep may not be necessary for adequate CPAP pressure titration, although we accept that the number of patients without REM sleep is relatively small ( $n=8$ ).

In keeping with the American Thoracic society recommendations (Phillipson & Remmers 1989) other investigators required an  $AHI > 30$  in the diagnostic half of the split-night before proceeding to CPAP titration (Fleury et al. 1994, Strollo et al. 1996, Sanders et al. 2000). In the current study 17 patients in the split-night group and 34 patients in the full night group had an  $AHI \leq 30$  on the diagnostic study. Median nightly CPAP use in these groups was similar. Comparison of Kaplan-Meier plots suggests a trend towards worse long-term compliance in those patients undergoing a split-night study (Fig. 5.2), but this was not statistically significant. Larger numbers of patients may be required to determine if CPAP titration should proceed in the second half of the night when there is mild severity disease on the diagnostic portion of the split-night study.

The independent predictors of long-term CPAP use were increasing pre-treatment ESS and decreasing TST in the diagnostic half of the study. Pre-treatment ESS, and

other measures of subjective daytime sleepiness, are established predictors of compliance with CPAP treatment as outlined in chapter 4.4. A short diagnostic TST may lead to better long-term use because this allows a longer time for CPAP titration which may result in a more accurate CPAP pressure determination (Yamashiro & Kryger 1995). However, a typical pattern of oxygen desaturation is associated with a shorter diagnostic TST, presumably because this makes it easier for the night nurses to decide to start CPAP titration. A shorter diagnostic TST may lead to better long-term use because oxygen desaturation is a marker of disease severity and a predictor of CPAP compliance (Pieters et al. 1996, Rolfe et al. 1991). Hence, it appears likely that the determinants of improved use, high ESS and low diagnostic TST, are both markers of severe SAHS.

Patients were not booked for split-night studies if there were symptoms of restless leg syndrome or symptoms suggestive of a diagnosis of narcolepsy. However, 5 patients had an elevated AHI and an increased frequency of leg jerks ( $>5/\text{hr}$ ) on the diagnostic half of the split-night study (as did 7 patients in the full night group). These patients were treated with CPAP alone with resolution of daytime sleepiness (all; post-treatment ESS  $\leq 7$ ). There were 4 patients who had symptoms that can be suggestive of narcolepsy but also occur in SAHS (particularly when there is severe daytime sleepiness), i.e., either vivid dreams or definite hypnagogic hallucinations (Guilleminault 1989). All these patients had classical symptoms of SAHS and markedly raised AHI's in the diagnostic portion of the split-night study (AHI=50-195 events/hr) and had resolution of daytime sleepiness with CPAP alone (post-

treatment  $ESS \leq 5$ ). Further diagnostic studies for narcolepsy have not been indicated in these patients.

The reasons for patients undergoing split-night studies were divided into 3 categories, with most studies being carried out for a 'classical' history of SAHS. Hence, our findings are most applicable to patients who present with classical symptoms of SAHS. The other main clinical group of patients studied had a good history of SAHS plus a supportive limited investigation. Although the number in this group was smaller, the reason for split-night study was not an independent predictor of CPAP use, indicating that these patients can be managed effectively with a split-night study.

The limitations of this study include the use of retrospective data. However, the split-night patients were a consecutive series and all data were accrued prospectively, reducing bias from retrospective analysis of studies. Furthermore, matching was performed using the split-night AHI and ESS, blinded to patient study outcomes. Because of the lack of good evidence for effectiveness of split-night studies only 49 patients had been booked during the study period. Nevertheless, the possibility of a selection bias seems unlikely since the patients booked for split-night studies were similar to matched full night study patients in important clinical characteristics (age, sex, ESS, symptom severity, and BMI) used to assess patients for the presence of SAHS (table 5.2).

## **5.5 Conclusions:**

As discussed in chapter 1.5.1 and 1.5.2, many different approaches to the diagnosis of SAHS using clinical features and anthropometric variables have been studied. It is, however, usually necessary to perform an overnight study of breathing during sleep to accurately diagnose SAHS. As indicated in chapter 1.7.3 there appear to be high levels of undiagnosed SAHS in the community. The use of split-night studies may allow more patients access to sleep laboratory services by reducing the number of nights to diagnose and treat SAHS in some patients. These are the first controlled long-term data showing that, among selected patients, this approach is as effective as the standard 2 full nights of diagnosis and treatment.

**CHAPTER 6 – THE EFFECT OF CPAP ON THE SLEEP  
QUALITY OF PATIENTS WITH SAHS AND THEIR  
PARTNERS**

## **6.1 Introduction:**

Most data on the effect of CPAP on the objective sleep quality of SAHS patients come from uncontrolled studies (Collard et al. 1996, Bonsignore et al. 1987, Fietze et al. 1997, Lamphere et al. 1989). These found improved PSG sleep quality after starting CPAP, however, there is no randomised placebo controlled evidence for this. A Medline and Embase literature search found only one placebo controlled study; this study did not show any difference in sleep indices between the CPAP and placebo treatment limbs (Loredo et al. 1999). There is also little information, and no randomised controlled data, on the effect on partners of treatment of patients with CPAP (Kiely & McNicholas 1997, Vagiakis et al. 1999, Beninati et al. 1999). Only one study has used objective measures of sleep quality in their assessments (Beninati et al. 1999).

Furthermore, our understanding of the factors that determine CPAP use and benefit from CPAP in SAHS is poor, and pre-treatment predictors that have been identified are weakly associated with these outcomes (discussed in chapter 1.4.7 and 4). Sleep architecture may play a role in determining which patients benefit from and use CPAP as suggested in some previous studies (Meurice et al. 1994, Waldhorn et al. 1990). There is some evidence that partners of SAHS patients may influence CPAP use (Hoy et al. 1999).

The main hypothesis of this study was that patients and partners of patients with SAHS would have improved sleep quality (the principal outcome measure being PSG sleep quality) when the patient received CPAP treatment. A secondary



hypothesis was that there would be improvements in the partners' quality of life and marital satisfaction with CPAP. We also sought to explore relationships between the sleep quality, of both patients with SAHS and their partners, and clinical outcomes from CPAP treatment.

## **6.2 Methods:**

### ***6.2.1 Protocol***

The study randomised SAHS patients and their partners (couples) to a crossover study of CPAP and placebo capsule treatment for the patient. After one month on each study limb assessments of sleep quality (and other relevant changes in partners) were assessed in both the patient and their partner. Baseline questionnaires were also sent to couples prior to recruitment in the crossover study. Patients and partners were asked to complete questionnaires separately. When couples agreed to take part in the crossover study the patient was randomised the morning after CPAP titration, using a random number table and sealed envelopes, to receive either placebo capsule (lactose, Nova Laboratories, Wigston, UK) or CPAP treatment. The treatment intervention was reversed during the subsequent month, with no washout period. Balanced block randomisation was used to ensure that the order of intervention was equal across the study group. CPAP treatment was given with a Sullivan Elite machine (ResMed Ltd., North Ryde, NSW, Australia) which gave a nightly assessment of CPAP use at the prescribed pressure. Placebo capsules were prescribed to be taken 1 in the evening and patients were told that the capsule treatment might improve upper airway muscle function in sleep; this was approved



by the local ethics sub-committee. All patients received standard education (chapter 3.2.2). Patients received a follow-up phone call 10 days after the start of each intervention and this call was used to troubleshoot problems with placebo or CPAP use.

At the end of each intervention patients and partners had simultaneous PSG monitoring of their sleep in the home, using the Compumedics P-series portable system (chapter 3.5). On the CPAP nights, the CPAP mask and headgear was carefully placed over the patient's monitoring electrodes – the use of CPAP did not affect the quality of recordings. The PSG monitoring was started at the couple's usual bedtime and stopped at their usual wake time. This was the time in bed (i.e., TRT) which was kept the same, as was the time of the week (i.e., week or weekend), on both limbs of the study. Couples were asked not to consume alcohol or caffeinated drinks for 6 hours before the start of the recording.

The study had the approval of the local ethics sub-committee. All patients gave written informed consent before starting the crossover study.

### ***6.2.2 Couples studied***

Consecutive patients with SAHS who were booked for CPAP treatment were approached and couples were recruited if they met the following criteria:

#### **Inclusion criteria:**

1. Patients with 2 or more symptoms of SAHS (Whyte et al. 1989)  
and
2. AHI>15events/hr on a sleep study recording EEG  
or  
>30 apnoeas and hypopnoeas/hr recorded on a limited study (non-EEG based,  
see chapter 3.1).
3. Patients had a bed-partner and they shared a bed  $\geq 2$  nights/week.

Exclusion criteria:

1. Medication use or co-existing disorder in either patient or partner that was likely to disturb sleep quality, including; sleep disorders such as narcolepsy or insomnia (defined among partners as regular use of hypnotic medications or reported sleeping<6hours/night), neurological disorders and severe chronic respiratory disease.
2. The patient or partner was doing regular overnight shift-work.
3. The patient or partner consumed > 21 standard units of alcohol/week.
4. The partner had been diagnosed with deafness or regularly used earplugs at night.

### **6.2.3 Study Outcomes – a) patients**

Objective sleep quality was assessed from home PSG studies. To explore relationships between sleep architecture and clinical outcomes we selected, *a priori*, 4 PSG indices that are commonly used and are physiologically important. These were: the SEI, the arousal index, time in stage 3+4 (minutes), and time in stage REM (minutes) (chapter 3.4). The following clinical outcomes were assessed: the change in feeling refreshed in the morning (between study limbs), change in ESS from placebo to 6-12 months of CPAP treatment, and the average nightly CPAP use after 6-12 months on CPAP (determined from in-built time clocks).

Patients were asked to rate how refreshed they felt the morning after home sleep studies, from completely unrefreshed to completely refreshed, using a 5-point Likert scale. Benefit to patients on CPAP compared to placebo study nights was assessed by subtracting the rating of refreshed after the placebo night from the rating after the CPAP night. More long-term benefit from CPAP was assessed by the change in 6-12 month ESS; calculated by subtracting the ESS after 6-12 months on CPAP treatment from the 1-month placebo ESS.

### **6.2.3 Study Outcomes – b) partners**

#### Baseline assessments

Partners' sleep quality and disturbance to sleep was assessed using the Pittsburgh Sleep Quality Inventory (PSQI) and with an in-house questionnaire (chapter 3.5.1,

appendix b). The partners' quality of life was assessed by the U.K. version of the Short Form 36 quality of life questionnaire (SF 36) (chapter 3.5.1). Couples were also asked questions about the main reason for seeking medical attention and who decided the patient needed medical attention (chapter 3.5.1, appendix b). A weighted score for 'partner decided' was calculated; with 1 scored for each time the partner was nominated by either patient or partner and a  $\frac{1}{2}$  if 'both equally' was nominated. The same scoring was used for 'patient decided' and the ratio 'partner decided' to 'patient decided' was calculated.

### Crossover study assessments

Objective sleep quality was assessed from home PSG studies. Subjective sleep quality was assessed with the PSQI and with an in-house questionnaire (appendix b) which asked couples about their sleep quality and sleep disturbance. The sleep disturbance from all causes was added to give a total score for sleep disturbance. Partner daytime sleepiness was assessed using the ESS and the Functional Outcomes of Sleep Quality (FOSQ) questionnaire (chapter 3.5.1).

Partners also completed the SF36 and the Enrich marital satisfaction questionnaire (chapter 3.5.1). The in-house questionnaire also asked partners to estimate the changes in their and the patients' sleep quality and daily functioning by making comparisons between the status in each intervention limb and the status before the study started. At the end of the study partners were asked which treatment they would prefer the patient to use.

The morning after sleep monitoring partners were given a 15-minute test of reaction time using a laptop computer (see chapter 3.5.2, SURT). To minimise practice effects they also performed the test for 15 minutes on the first study evening. Partners were also asked to rate how refreshed they felt in the morning, from completely unrefreshed to completely refreshed.

All sleep studies were analysed by the researcher blind to the subject name, intervention limb, respiratory, and oxygenation data. Sleep was scored as outlined in chapter 3.4. The quality of the recorded signals was assessed based on criteria used in the SHHS (Redline et al. 1998b).

#### ***6.2.4 Statistical analysis***

Statistical analyses were performed using the SPSS statistical software package, version 9 (SPSS Inc, Chicago, IL). When data were normally distributed comparisons were made using t tests. Data that were ordinal or were not normally distributed were compared using the Mann-Whitney test for between-group comparisons and the Wilcoxon test for within-group comparisons. The Chi-squared test was used to compare categorical and ordinal data and the sign test was used for dichotomous outcomes (i.e., comparison of 2 treatments) from a single sample. Correlations were calculated using Pearson's correlation coefficient for normal data and Spearman's rank correlation for non-parametric data.

Comparisons on normal data from the crossover trial were made using the General Linear Model repeated measures analysis of variance (GLM) with treatment as a

within subject factor and order as a between subject factor (Hills & Armitage 1979). Treatment  $\times$  treatment order (differential carryover) effects were managed as recommended, by making unpaired comparisons using first limb data only (Hills & Armitage 1979). GLM assumptions were verified for all analyses. It was an *a priori* postulate that patient's CPAP use would be an important determinant of the effect of CPAP on the partner's sleep quality and PSG sleep quality outcomes were re-analysed using CPAP use for the month as a co-variable in the above model. This approach was used to remove the variance in the model due to CPAP use. All tests required a two-tailed p value  $\leq 0.05$  for statistical significance.

Before starting this study a power calculation was made using arousal index data from our data on the effects of tone induced sleep fragmentation on normal subjects (Martin et al. 1996). Tones were given every 2 minutes to produce arousals at a frequency mimicking that experienced by a typical SAHS patient (35 events/hour). We estimated that a clinically relevant change in daytime sleepiness in partners would occur if arousals induced by external stimuli, such as noise, were reduced by 5 arousals/hr. With  $\alpha=0.05$  and power =90% ( $\beta = 10\%$ ) we required 22 patients in the crossover study for an estimated effect size of interest of 5 arousals/hr and standard deviation of within pair difference of 5.9 arousals/hr (Florey 1993).

## **6.3 Results:**

### ***6.3.1 Couples studied***

107 couples met the inclusion criteria during 9 months of study recruitment. Of these 107, couples were excluded from the study because they had co-existing disease/medications likely to disturb sleep quality (n=23) or for other reasons (n=13), such as regular shift work. The remaining 71 eligible couples were sent baseline questionnaires and 49 patients/46 partners completed them. Twelve couples were excluded from the crossover study of the effect of CPAP versus placebo on objective sleep quality because there was clinical concern about driving problems due to sleepiness. This left 59 couples eligible for the crossover study. Twenty-three patients started the crossover study and 22 completed. The median (IQR) closed airway CPAP titration AHI was 3.4 (2.3-7.4) /hr. One patient dropped out of the crossover study (AHI=125 events/hr, ESS=13) shortly after starting the first (CPAP) limb and could not be included in the crossover analysis. Thirty-six patients declined to participate in the crossover study because of inconvenience or reluctance to be monitored in the home. Patients who declined the crossover study were similar to those who agreed to take part (table 6.1).



Table 6.1: Characteristics of patients agreeing to the crossover study compared with patients refusing the crossover study.

Patient characteristics	Crossover study patients (n=23)	Crossover study refusers (n=36)	p value
Mean age (+/-sd), yrs	53 (+/-11)	51 (+/-10)	0.4
Number male	20	29	0.7
Mean BMI (+/-sd)	31 (+/-5)	31 (+/-5)	0.8
Median ESS (IQR)	14 (10-17)	12 (8-16)	0.3
Median AHI/AH* (IQR), events/hr	40 (25-65)	44 (32-56)	0.7
Mean CPAP pressure (+/-sd), cm H <sub>2</sub> O	10 (+/-3)	9 (+/-2)	0.2

Abbreviations: sd = standard deviation, IQR = interquartile range

\* AH = Number of apnoeas and hypopnoeas per hour of study recording (Limited sleep studies)

### 6.3.2 Crossover study results – patients’ sleep quality

The quality of the patients’ PSG studies for assessing EEG variables were ‘outstanding’ (n=40) or ‘excellent’ (n=3) based on the criteria used in the SHHS (Redline et al. 1998b). In the remaining study the battery ran out after 4 hours and only the first 4 hours of data were compared. The median (IQR) nightly CPAP use during the study was 4.5 (2.6-6.2) hrs/night. The median (IQR) CPAP use on the study night of 7.2 (6.4-7.9) hrs/night was higher than the median nightly use for the month ( $p<0.001$ ).

On the CPAP night there was significantly less stage 1, more stage 3+4, and a lower arousal index than on the placebo night (table 6.2). Analysis of normally distributed

data (stage REM) did not show any evidence of order (acclimatisation) effects or of treatment by order interactions. Patients were more refreshed after the CPAP night than the placebo night [Median (IQR) refreshed; CPAP 4 (3-5), placebo 3 (2-3.2),  $p=0.002$ ].

Table 6.2: Comparisons of patients' polysomnographic sleep quality on each intervention limb in the crossover trial.

Polysomnographic variables	Placebo (n=22)	CPAP (n=22)	P value
Mean total recording time (+/-sd), mins	489 (+/-45)	489 (+/-45)	1
Median sleep latency (IQR), mins	19 (12-32)	15 (9-28)	0.6
Median awake time in sleep period (IQR), mins	81 (45-113)	59 (34-95)	0.4
Median SEI (IQR), %	77 (69-81)	80 (69-85)	0.4
Median latency to stage 3+4 (IQR), mins	22 (13-34)	18 (13-24)	0.4
Median stage 2 (IQR), mins	239 (173-258)	213 (186-251)	0.3
Median latency to stage REM (IQR), mins	79 (57-129)	66 (55-95)	0.2
Mean stage REM (+/-sd), mins	74 (+/-29)	86 (+/-30)	0.1
Median stage 1 (IQR), mins	24 (14-34)	12 (6-19)	0.03
Median stage 3/4 (IQR), mins	23 (12-39)	41 (30-67)	0.007
Median arousal index (IQR), events/hr	45 (32-77)	21 (17-31)	<0.001

Abbreviations: SEI = sleep efficiency index

Follow-up outcomes, at 6-12 months [median (IQR)=7.5 (6-9) months], were available for all participants. The median (IQR) CPAP use at 6-12 months of 3.8

(0.8-5.4) hrs/night was similar to that during the study month ( $p=0.1$ ). The median (IQR) ESS on placebo was 13 (7.8-15.5); with lower values at the end of the CPAP study month of 6 (4.8-11) ( $p<0.001$ ) and after 6-12 months on CPAP of 7 (4.8-10.8) ( $p=0.002$ ).

The change in PSG variables on the study nights correlated moderately strongly with the change in feeling refreshed the morning after these nights (all variables;  $r=0.4-0.5$ ,  $p\leq 0.02$ ). Change in feeling refreshed correlated with change in ESS at 6-12 month ( $r=0.63$ ,  $p=0.002$ ) but did not correlate with CPAP use at 6-12 months. The SEI on the CPAP night was strongly correlated with change in ESS at 6-12 months (figure 6.1) and was correlated with 6-12 month CPAP use (figure 6.2). Other CPAP study night PSG variables correlated with 6-12 month change in ESS, and the weakest of these correlations was with arousal index (figures 6.3-6.5). The only correlations between changes in PSG variables and 6-12 month outcomes were between change in arousal index and change in stage 3+4 with 6-12 month change in ESS (stage 3+4;  $r=0.54$ ,  $p=0.01$ , arousal index;  $r=0.45$ ,  $p=0.03$ ). There were no significant correlations between PSG variables on placebo and 6-12 month outcomes.

Figure 6.1

Change in Epworth sleepiness score after 6-12 months of CPAP treatment versus CPAP sleep efficiency index (at 1 month).

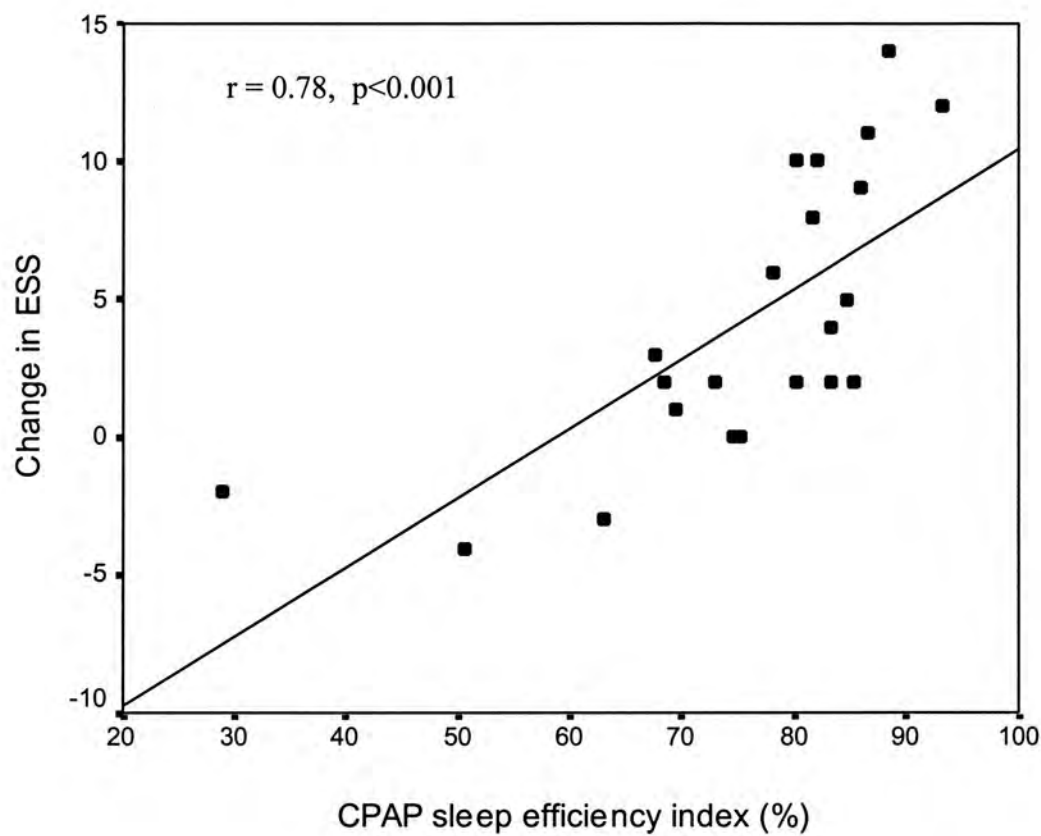


Figure 6.2

Median nightly CPAP use at 6-12 months versus CPAP sleep efficiency index (at 1 month).

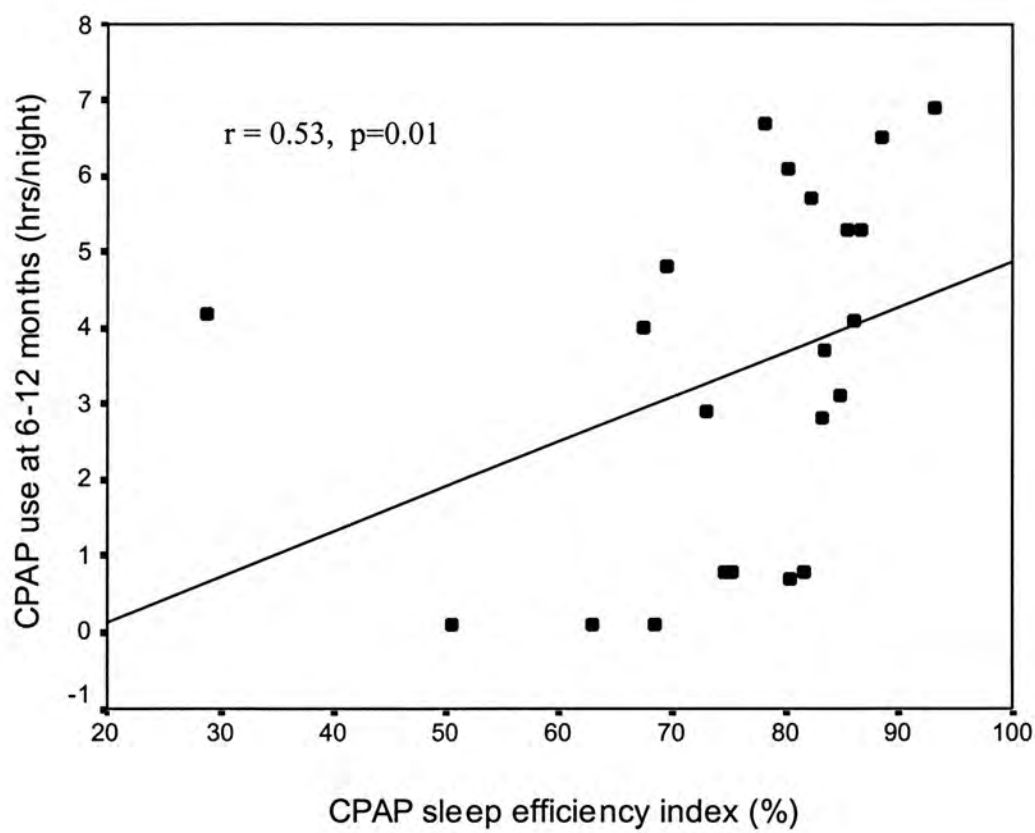


Figure 6.3

Change in Epworth sleepiness score after 6-12 months of CPAP treatment versus CPAP stage REM (at 1 month).

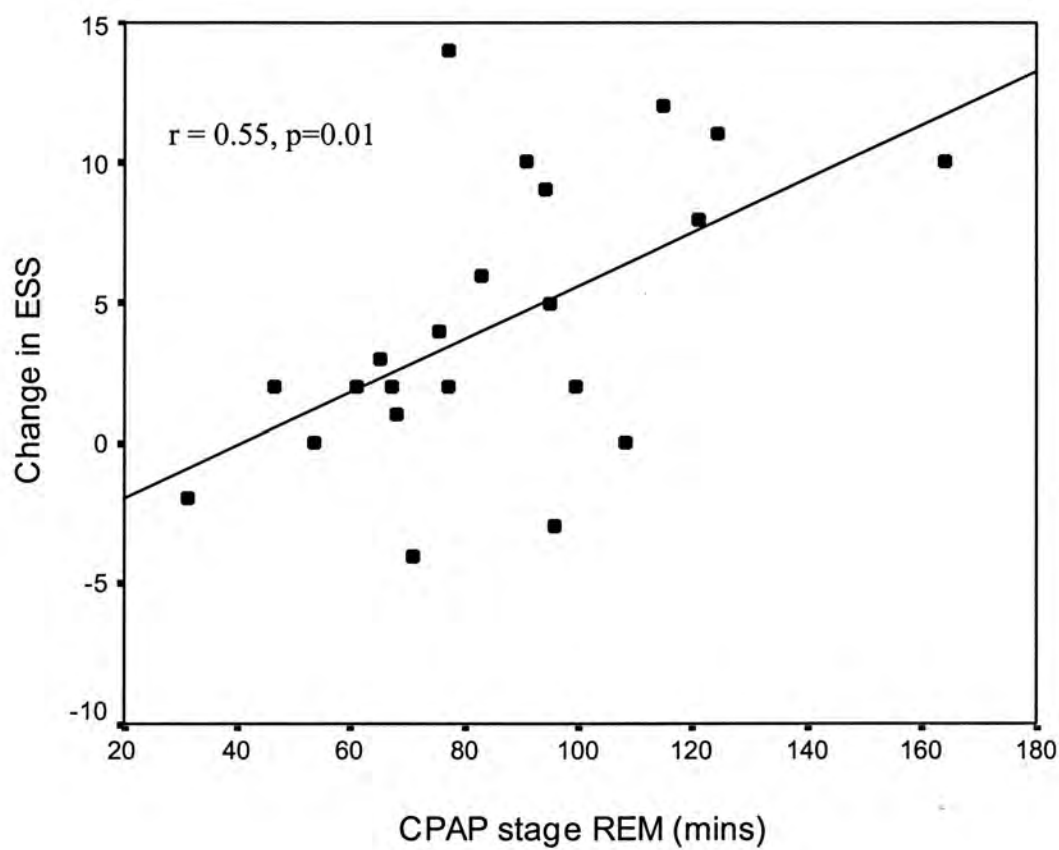


Figure 6.4

Change in Epworth sleepiness score after 6-12 months of CPAP treatment versus CPAP stage 3+4 (at 1 month).

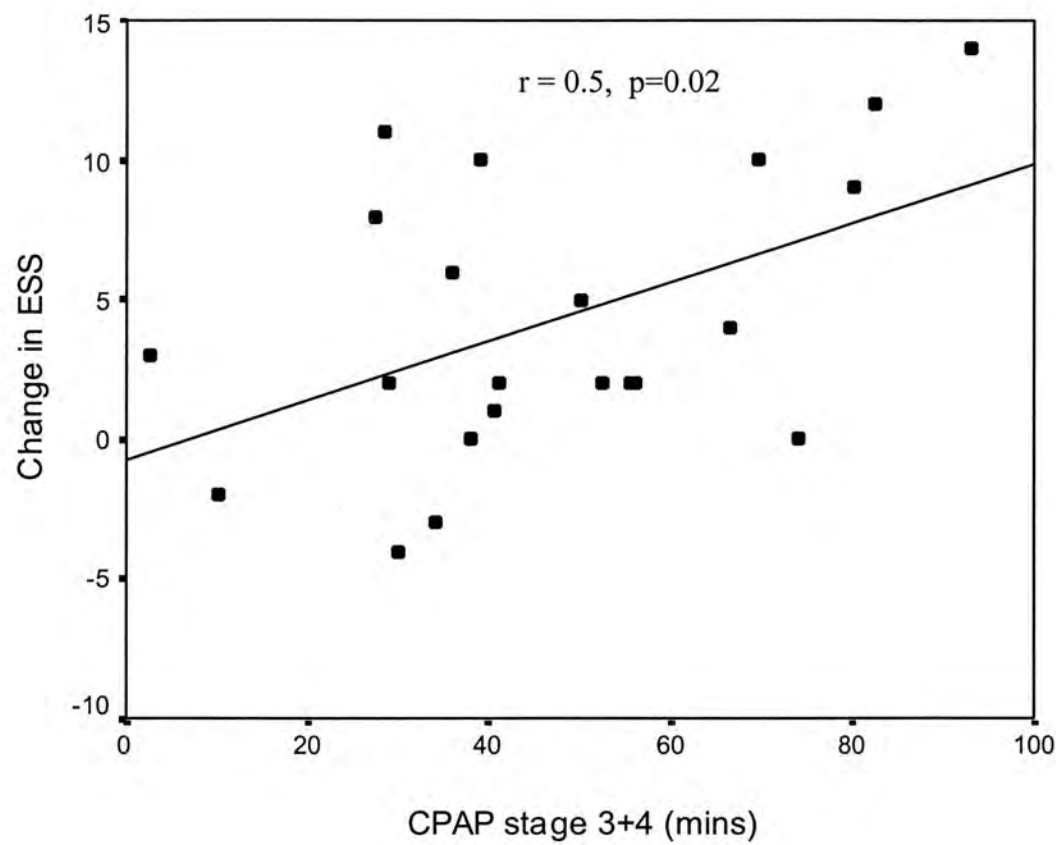
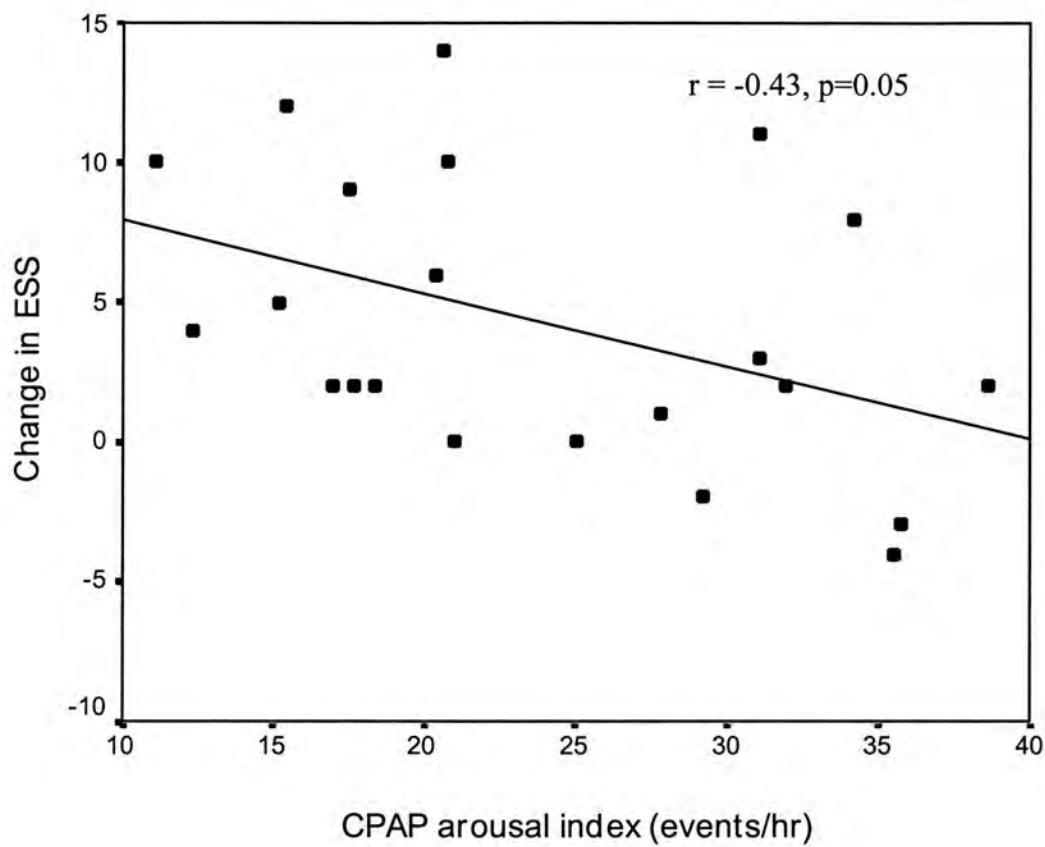




Figure 6.5

Change in Epworth sleepiness score after 6-12 months of CPAP treatment versus CPAP arousal index (at 1 month).



### *6.3.3 Crossover study results – partners' sleep quality*

The quality of the partners' PSG studies for assessing EEG variables were 'outstanding' (n=41) or 'excellent' (n=3) based on the criteria used in the SHHS (Redline et al. 1998b). No partner had a diagnosis of the SAHS or restless leg syndrome (one had mild PLMS= 7.8 events/hr).

Partners had similar objective sleep quality on CPAP and placebo study nights (table 6.3). There were no order (learning/acclimatization) effects. Only sleep latency showed a significant treatment  $\times$  treatment order (differential carryover) effect ( $p=0.02$ ) and unpaired comparisons were made on first limb data for this variable (Hills & Armitage 1979). Measures of reaction times after monitoring did not differ between intervention limbs, apart from a weak trend for the partners' mean reciprocal reaction time being better on the CPAP limb (table 6.3).

Mean CPAP use for the month was a significant covariate in the GLM model of PSG partner SEI ( $p=0.01$ ) and arousal index ( $p=0.01$ ), but not of stage 3+4. Re-analysis with mean CPAP use (for the month) as a co-variable in the GLM model showed that partners had a higher SEI ( $p=0.03$ ) and a trend to lower arousal index ( $p=0.06$ ) on the CPAP limb. There was a positive correlation between partner change in in-house sleep quality (from pre-study to CPAP) and CPAP use ( $r=0.5$ ,  $p=0.01$ ). The change in the partners' in-house sleep quality as assessed by the partner showed a strong correlation with this assessment by the patient ( $r=0.6$ ,  $p<0.001$ ). The change in the patients' SEI (CPAP-placebo) correlated positively

with the change in the partners' SEI ( $r=0.54$ ,  $p=0.01$ ), but there was no correlation for changes in arousal index or changes in stage 3+4 between patients and partners.

Partners' subjective sleep quality, assessed over 1 month, was better on the CPAP limb on the in-house questionnaire and there was a trend to better sleep quality on PSQI (table 6.4). Partners reported less total disturbance to sleep on the CPAP limb (table 6.4), but 17 partners reported disturbance from CPAP and in 6 this was moderate or severe. The main cause of disturbance from CPAP was noise from the machine ( $n=10/17$ ), or cold air ( $n=3/17$ ) (4 did not give a cause).

Table 6.3

Comparisons of partners' polysomnographic sleep quality, simple reaction time, and feeling refreshed in the morning after monitoring on each intervention limb in the crossover trial.

Study night & morning assessments	CPAP limb (n=22*)	Placebo limb (n= 22*)	p value
Mean TRT (+/-sd), mins	489 (+/-45)	489 (+/-45)	1
Mean sleep latency (+/-sd), mins	26.3 (+/-13)	32.6 (+/-15)	0.3
Mean SEI <sup>†</sup> (+/-sd), %	78% (11%)	77% (11%)	0.8
Mean arousal index (+/-sd), events/hr sleep	24 (+/-11)	25 (+/-12)	0.4
Mean time in stage 3 and 4 (+/-sd), minutes	43 (+/-24)	43 (+/-26)	0.9
Mean time in stage REM (+/-sd), minutes	83 (+/-28)	90 (+/-25)	0.9
Median SURT response time (IQR), seconds	0.33 (0.28-0.39)	0.36 (0.33-0.38)	0.4
Mean reciprocal SURT response time (+/-sd), seconds <sup>-1</sup>	2.9 (+/-0.5)	2.9 (+/-0.4)	0.1 <sup>††</sup>
Median 95 <sup>th</sup> percentile SURT response time (IQR), seconds	0.47 (0.44-0.6)	0.50 (0.44-0.58)	0.5
Median refreshed in morning (IQR)**	3 (2.5-4)	3 (2-4)	0.4

Abbreviations: SEI=sleep efficiency index, TRT=total recording time, SURT=simple unprepared reaction time

\* Sleep latency data was compared during the first limb of the study only because of a treatment × treatment order effect (see 6.2.4, statistical analysis)

† SEI was calculated as total sleep time/ total recording time

†† There was a weak trend favouring better (quicker) partner mean reciprocal reaction times on the CPAP limb

\*\* Maximally refreshed = 5, maximally unrefreshed = 1

Table 6.4

Comparisons of partners' questionnaire responses in each intervention month of the crossover trial.

Partner questionnaire responses	CPAP limb	Placebo limb	p value
Median subjective sleep quality score for month (IQR)	1 (1-2)	1 (0.75-2)	0.05
Median PSQI score (IQR)*	6 (4-10.5)	7 (4.5-11)	0.08
Median total sleep disturbance score for month (IQR)	2 (1.5-5)	5 (3-6)	0.03
Mean ESS (+/-sd)	6.5 (+/-4.5)	5.9 (+/-4.3)	0.3
Median FOSQ (IQR)	14.5 (12.9-15.5)	14.7 (12.9-15.9)	0.7
Mean physical summary score SF36 (+/-sd)	44.0 (+/-15)	43.5 (+/-13)	0.7
Mean mental summary score SF 36 (+/-sd)	46.8 (+/-9)	48.2 (+/-9)	0.4
Median ENRICH score (IQR)	45 (39-56)	51 (31-58)	0.6
Median partners' reported change in patient's sleep quality (IQR)	2 (1-3)	0 (0-1)	0.007
Median partners' reported change in patient's daily functioning (IQR)	1 (0-3)	0 (0-1)	0.03

Abbreviations: PSQI=Pittsburgh sleep quality index, ESS=Epworth sleepiness score, FOSQ=Functional outcomes of sleepiness questionnaire, SF36=Short form 36 questionnaire, ENRICH=Evaluation and nurturing relationship issues, communication and happiness Marital Satisfaction Scale

\* PSQI: higher scores = worse sleep quality

### ***6.3.4 Crossover study results – partners’ quality of life and other changes***

Partner daytime subjective sleepiness, quality of life, and marital satisfaction did not differ between limbs (table 6.4). Partners reported greater improvement in the patients’ sleep quality and daily functioning on CPAP than on placebo (table 6.4). Eighteen partners said they prefer the patient was treated with CPAP and 4 said they would prefer the (placebo) “capsule” was used ( $p=0.01$ ). The median (IQR) number of nights/week couples shared a bed was unchanged during the study [CPAP=7 (6-7); placebo=7 (5-7),  $p=0.4$ ].

Follow-up SF36 and Enrich questionnaires at 6-12 months on CPAP ( $n=18$ ) were not different to placebo at 1 month [Mean (+/-sd): 6 month SF36 physical component score=42(+/-15),  $p=0.6$ ; 6 month mental component score=47.6(+/-10),  $p=0.8$ ; Median (IQR) 6-12 month Enrich score=49(35-57),  $p=0.8$ ].

### ***6.3.5 Baseline questionnaire results***

Table 6.5 compares the baseline clinical characteristics of all patients who filled in questionnaires with those recruited to the crossover study and compares them with those not filling in questionnaire. These groups were similar. Couples in the crossover trial were also similar to those completing baseline questionnaires in: who decided to seek medical attention, the main reason for seeking medical attention, disturbance from patient snoring/apnoeas/restlessness, and sleep quality (in-house and PSQI) (all  $p>0.2$ ).

Table 6.5

Comparisons of baseline patient characteristics for those completing questionnaires with participants in the crossover trial and those not completing questionnaires.

Patient Baseline characteristics	Questionnaire participants (n=51)	Crossover trial participants (n=23)	p* value	No questionnaires (n=20)	p <sup>†</sup> value
Mean age (+/-sd), years	53 (11)	53 (11)	0.8	48 (8)	0.1
Number male sex	44	20	0.6	18	0.7
Mean BMI (+/-sd), kg/m <sup>2</sup>	32 (5)	31 (5)	0.8	32 (5)	1.0
Median AHI/AH <sup>††</sup> (IQR), events/hr	41 (28-60)	40 (25-65)	0.9	37 (28-69)	0.7
Mean ESS (+/-sd)	12 (5)	13 (5)	0.8	15 (3)	0.1
Mean CPAP pressure (+/-sd), cm H <sub>2</sub> O	9 (2)	10 (3)	1.0	9 (2)	0.4

\* p value for questionnaire participants compared with crossover trial participants

† p value for questionnaire participants compared with questionnaire non-participants

†† Number of apnoeas and hypopnoeas per hour of study recording (Limited sleep studies)

The PSQI showed 14/41 (34%) partners had 'good' sleep whereas 8/46 (17%) had 'good' or 'excellent' sleep by in-house questionnaire. Moderate or severe sleep disturbance from snoring, apnoeas, and restlessness was reported by 32 (69%), 25 (54%) and 26 (55%) partners, respectively. Comparison of the partners' mean PSQI



(+/-sd) scores with published normative values found their sleep quality was worse than the normal population [partners; 7.9(+/- 3.6), normals; 2.7(+/-1.7),  $p<0.001$ ].

Baseline SF36 questionnaire results were sex weighted and compared with normal values for the middle-aged UK population (Jenkinson et al. 1996). This showed that partners (n=41) had poorer SF36 role emotional ( $p<0.001$ ), energy/vitality ( $p<0.001$ ), role physical ( $p<0.001$ ), bodily pain ( $p=0.002$ ), physical functioning ( $p=0.002$ ) and social functioning ( $p=0.02$ ) with a trend to poorer mental health ( $p=0.08$ ) and general health ( $p=0.07$ ). Mean (+/-sd) physical and mental component summary scores were also worse than UK 'normals' [Physical: partners: 40.5(+/-14.2), normals: 49.3(+/-10.2),  $p<0.001$ ]; Mental: partners: 45.5(+/-11.3), normals: 49.2(+/-10.3),  $p=0.02$ ].

The main reason patients sought medical attention was almost evenly split between snoring or concern about apnoeas (24/49) and sleepiness/tiredness (25/49). Partners made the decision to seek medical attention more often than patients (partner:patient = 1.9:1).

#### **6.4 Discussion:**

This is the first randomised placebo controlled study to show that SAHS patients have improved sleep architecture after a month of CPAP treatment. CPAP treatment resulted in better sleep quality with fewer arousals, less light (stage 1) sleep, and more deep (stage 3+4) sleep. Although unsurprising, this adds important new randomised placebo controlled evidence of efficacy of CPAP in the SAHS. CPAP

treatment for SAHS improved partners' subjective sleep quality and sleep disturbance, but there was no evidence of improved objective sleep quality or benefit on validated measures of quality of life or marital satisfaction. The study also shows that partners perceive benefits to patients' sleep quality and daily function with CPAP treatment.

This study showed that median nightly CPAP use at 6-12 months had little correlation with the patient's objective sleep quality (only SEI on CPAP was related to subsequent CPAP use). Commonly used PSG sleep indices measured after 1 month of acclimatisation to CPAP treatment were related to benefit at 6-12 months, as assessed by the change in ESS from placebo. SEI during CPAP was the best predictor of subsequent benefit. There was a positive association between the partners' sleep quality and the patients' CPAP use during the crossover study.

#### ***6.4.1 CPAP's effects on sleep quality of SAHS patients***

Our data on the effect of CPAP on sleep quality confirms and extends a number of uncontrolled studies that have measured PSG sleep indices before and after SAHS patients started CPAP treatment. Some found an increased time in stage 3+4 (Collard et al. 1996, Fietze et al. 1997, Lamphere et al. 1989) and stage REM (Bonsignore et al. 1987, Collard et al. 1996, Lamphere et al. 1989), and reduced time in stage 1 (Bonsignore et al. 1987, Collard et al. 1996, Fietze et al. 1997, Lamphere et al. 1989). Others found an increased stage 2 (Lamphere et al. 1989), reduced stage REM latency (Fietze et al. 1997) and stage 3+4 sleep latency (Fietze et al. 1997). However, such 'before and after' studies do not take into account first-

night effects, which can mean that sleep quality improves after the first study night because of acclimatisation (Toussaint et al. 1995). Also, placebo effects are not taken into account in 'before and after' studies.

The current randomised placebo controlled study has now confirmed some of these changes but found no significant increase in REM sleep. The changes in stage REM reported in 'before and after' studies were often small [e.g. CPAP increased stage REM by 4.1% of TST (Collard et al. 1996)] and acclimatisation effects may explain this earlier finding. Alternatively, REM sleep suppression in the untreated state could be a function of SAHS severity. Our patients had a median AHI of 40 events/hr which was appreciably lower than the RDI's of patients in studies that have shown more stage REM on CPAP (Collard et al. 1996, Lamphere et al. 1989, Bonsignore et al. 1987). One study of first night effects (Toussaint et al. 1995) found stage REM latency decreased on 2<sup>nd</sup> and 3<sup>rd</sup> nights, possibly contributing to the shortened REM latency with CPAP found in 'before and after' studies.

The only other placebo controlled trial of the effect of CPAP on sleep quality that we can find showed no differences in sleep quality after 7 days on therapeutic versus sub-therapeutic CPAP (Loreda et al. 1999). Significant changes with time, but not with treatment, were found in that study, and these are likely to reflect first-night effects. In the current study all patients had had previous (in-laboratory) sleep studies and assessments were done using home studies which have small first-night effects (Coates et al. 1981, Sharpley et al. 1988). Furthermore, we reduced the potential bias of first-night effects by using balanced blocks in the randomisation of the order of intervention and we found no evidence of first night (acclimatisation)

effects on our data. Loredó and colleagues (Loredó et al. 1999) used repeated measures to compare two different groups of patients whereas in the current study each patient acted as their own control, reducing variability from between-group differences. Although the number of patients assessed in this earlier study was similar to the current study the increased statistical power of the crossover design may have been important. Loredó and colleagues (Loredó et al. 1999) assessed changes after 7 days, which might be before sleep benefits are maximal.

An assessment of feeling refreshed in the morning was used as a measure of the quality of the previous night's sleep. This measure aims to examine the effect of interventions on the monitoring nights themselves, which would be less affected by the previous CPAP use pattern. In this study nearly all patients used their CPAP treatment on the monitoring night as prescribed (i.e., "all night") whereas use over the whole study month was more variable. When patients used CPAP largely as prescribed, they felt more refreshed in the morning than after the placebo night. The changes in feeling refreshed (CPAP minus placebo) also predicted subsequent benefit from CPAP in daytime sleepiness. Further, changes in feeling refreshed in the morning was associated with changes in all of the 4 commonly used sleep indices to a similar degree, suggesting that feeling refreshed in the morning is a reasonable gauge of the sleep architecture during the previous night. Improvement in SAHS symptoms on starting CPAP can be dramatic (Sullivan & Issa 1985) and, although not investigated in this study, changes in feeling refreshed in the morning after initial CPAP titration may provide an early clue to future benefit.

Two outcomes, measured after 6-12 months of CPAP treatment, were used to assess more long-term benefit from CPAP. One of these, nightly CPAP use, is a widely used measure. As indicated in chapter 2.5.4, there is no known lower threshold for benefit and there may be considerable individual variability in the nightly use needed to gain benefit. Median nightly CPAP use was similar to previous values from our centre (Engleman et al. 1998) and to values in the literature (Reeves-Hoche et al. 1994, Pieters et al. 1996). We also assessed the change in ESS from placebo to 6-12 months on CPAP as a more direct measure of long term benefit from CPAP treatment. There were large improvements in daytime sleepiness seen after 1 month of CPAP treatment, which were sustained at 6-12 months.

Sleep quality indices on CPAP nights were the best predictors of change in ESS from placebo to 6-12 months on CPAP, with the SEI showing a strong relationship. Surprisingly, changes in sleep quality between placebo and CPAP were less well correlated with benefit, indicating that sleep quality during treatment has a more important effect on benefit than the change in sleep quality with treatment. Some recent studies have shown that intelligent CPAP pressure adjustment (chapter 2.3.1) results in better clinical outcomes than fixed pressure CPAP and in some of these (Konerman et al. 1998, Randerath et al. 1999, Scharf et al. 1996) intelligent CPAP was also associated with improved sleep quality. This is in keeping with our findings that good sleep quality on CPAP treatment predicts subsequent benefit from treatment. If this is indeed a robust causal link, then developing CPAP machines that minimise sleep disturbance should improve clinical outcome for patients with SAHS. Sleep indices on placebo did not predict any subsequent treatment outcomes and this might be because sleep quality on placebo is influenced



by many factors other than SAHS. Apart from SEI on the CPAP study night, sleep indices did not correlate with 6-12 month median nightly use of CPAP; emphasising that different factors seem to determine nightly use to those determining benefit in daytime sleepiness.

Sleep architecture is associated with subjective sleep quality in normal subjects (Akerstedt et al. 1997) and to objective sleepiness in those with sleep disorders (Stepanski et al. 1984, Bedard et al. 1991). Further, among patients with SAHS the arousal index is inversely correlated with the amount of stage 3+4 sleep and stage REM sleep (expressed as a percentage of TST) (Collard et al. 1996). Experimental sleep fragmentation (Martin et al. 1996) induces sleep architecture changes of decreased stage 3+4 and stage REM, with a trend to increased stage wake. The current study found that benefit from CPAP (in terms of daytime sleepiness) was related to the arousal index on CPAP but more strongly related to other indices of sleep architecture on CPAP. Changes in arousal index and in stage 3+4 sleep were related to benefit, but again the stronger correlation was with change in stage 3+4. These findings suggest that the effect of CPAP on sleep architecture may be more important than its effect on arousal frequency in determining benefit from and use of CPAP.

#### ***6.4.2 CPAP's effects on sleep quality and quality of life of partners of patients with SAHS***

Considering the high baseline levels of sleep disturbance and poor sleep quality reported by partners we were surprised to find no improvement in their objective sleep quality when patients received CPAP treatment. Baseline comparisons (table 6.5, in-house questionnaires) do not suggest a selection bias affecting those participating in the crossover study. A possible explanation for the lack of benefit to partners' objective sleep quality from CPAP could be inadequate study power. We used a crossover design to increase the power of the study and our calculations indicated that there was adequate power to detect benefit in our principal outcome measure. It may be that significant disturbance to the partners' sleep from the patients' SAHS is irregular (but well remembered); in this case a much larger sample size would be needed than was possible in this study. Restrictions on consumption of alcohol/caffeinated drinks on PSG study nights may have meant that SAHS symptoms were milder on study nights than usual nights (Issa & Sullivan 1982). A recent study by Benaniti and colleagues (Beninati et al. 1999) measured objective sleep quality in 10 partners in the laboratory while sharing a bed with the patient. The patient was treated with CPAP in the second half of the night. Although this paper shows that partners may have improved sleep quality with CPAP, the numbers were small and it is unclear if unselected couples were recruited. Further, there is also no allowance for acclimatisation from the first to the second half of the night and no placebo control.



PSG recordings were technically very good and studies were conducted in the home environment. There were no order effects, indicating little alteration of the partners' sleep architecture from first-night effects. Others too (Coates et al. 1981, Sharpley et al. 1988) found minimal evidence of first-night effects from home sleep studies on normal subjects. The lack of benefit in assessments of partner feeling refreshed and tests of reaction time on the morning after monitoring (table 6.3) is consistent with the PSG assessment of sleep quality.

In previous studies (Kiely & McNicholas 1997, Vagiakis et al. 1999) there were improvements in the partners' subjective sleep quality, quality of life, alertness, and mood when patients were treated with CPAP. In one study (Vagiakis et al. 1999) there were also reported improvements in marital relationships. Neither of these studies incorporated a control group (to allow for placebo effects) or validated questionnaires. One of these studies (Kiely & McNicholas 1997) was retrospective and may have had recall and selection bias. The current study has used a randomised-controlled design and confirms an improvement only in partner subjective sleep quality, when patients receive CPAP treatment.

The lack of benefit to partners' quality of life may be, in part, because we used a standard questionnaire (i.e., SF36) that may not be sensitive to some of the benefits experienced by partners. Partners were aware that CPAP had improved the patients' sleep quality and daily function and this would be expected to have, at least, indirect benefits to the partner. The time of this study may not be long enough to see changes to partner quality of life and marital satisfaction from CPAP treatment. However, our 6-12 month follow-up questionnaires did not find subsequent

improvement in these measures. It is possible that SAHS symptoms reported by partners might not be the cause of the impairment in their sleep quality or quality of life, in which case treatment of the patient's symptoms would not benefit the partner.

In this study patients frequently presented to medical attention at the request of the partner and for symptoms that mainly affect the partner. It seems likely that partners would also influence patient CPAP use. Evidence for this comes from a recent study (Hoy et al. 1999), which found that CPAP use was lower among patients whose partners ask them to seek treatment. The current study adds further evidence by showing a positive association between partner-reported changes (from pre-study) in their sleep quality due to CPAP and patients' CPAP use. Although CPAP was not associated with improved objective sleep quality in the group of partners as whole, entering CPAP use as a co-variable showed there was heterogeneity of benefit by CPAP use. Further, there was an association between improvements in sleep quality (SEI) among patients on CPAP and improved partner sleep quality. Causation has not been shown but these findings suggest that partners gain benefit when CPAP use is good and/or that partners influence patients to use CPAP depending on the partners' perceived sleep quality with CPAP.

#### ***6.4.3 Partners' sleep quality and quality of life***

A major finding of the current study is that partners of SAHS patients have poor sleep quality and poor quality of life. An early study by Cartwright and colleagues (Cartwright & Knight 1987) compared a control group of divorced spouses (n=7)

with married couples (n=10) from the same pool of SAHS patients. They found that the married partners appeared (no statistical analysis was reported) to show worse adjustment in the marital and social/leisure area than the normal population. Using an Illness Intrusiveness rating scale, Shapiro and colleagues (Shapiro et al. 1999) found that SAHS interferes with couples' quality of life domains with similar intrusiveness to that occurring in end-stage renal disease. Ulfberg and colleagues (Ulfberg et al. 2000) examined questionnaire responses (n=728) from a random sample of 1,000 women in Sweden and found that loud snoring (in the husband) was associated with partner symptoms of insomnia, sleepiness, morning tiredness, and headache. The current study extends the previous findings by using well-validated questionnaires to estimate the extent of impairment in sleep quality and quality of life in partners of patients with laboratory diagnosed SAHS.

#### ***6.4.4 Study limitations***

Potential limitations of this study include the use of a capsule as a placebo and the increased CPAP use on the night of study. It has been argued that a capsule placebo may not be the most appropriate placebo for CPAP treatment (Wright et al. 1997). We believe that a placebo capsule is a valid placebo provided it is actively "sold" to patients as a possible therapeutic agent, as in this study. Sub-therapeutic CPAP is another usable placebo but we remain concerned that it could have worsened patients' sleep quality (due to sleeping with an ineffective encumbrance on one's face), particularly among less severe patients. This could have led, by itself, to a spurious finding of improved sleep architecture, among patients, from therapeutic CPAP. In studying the sleep quality of partners of patients with SAHS we aimed for

a comparison of the partners' sleep when the patient is treated with CPAP compared to no CPAP – when patients would cause potential disturbance from snoring and apnoeas. Comparison with subtherapeutic CPAP may have 'masked' this noise disturbance.

In this study we allowed 1 month for patients to acclimatise to CPAP, and all patients used CPAP for at least 25 hrs prior to assessment. The improved sleep quality among SAHS patients applies to nights of generally good CPAP use; the benefit on other nights of lesser use may be less. However, the study clearly shows that improved patient sleep quality is attainable with CPAP.

### **6.5 Conclusions:**

We have shown, in a randomised placebo controlled trial, that SAHS patients have improved sleep quality on CPAP; extending the growing randomised placebo controlled evidence of benefit from CPAP. While CPAP treatment usually benefits patients the benefit to partners is less clear. We were unable to demonstrate that CPAP improves the partners' objective sleep quality, although they had improved subjective sleep quality and perceived less total sleep disturbance (over a month).

Patients with good sleep architecture on CPAP will report subsequent benefit in daytime sleepiness. This suggests that improvements to treatment, such as the use of intelligent CPAP, that can improve patients' sleep quality, will also increase the clinical benefit to patients from CPAP. Partners may also benefit from quieter and

less intrusive CPAP machines because about one quarter of partners reported that CPAP machines caused them moderate-severe sleep disturbance.

This study found further evidence that partners of patients with SAHS have very poor sleep quality (apparently due to patients' nocturnal SAHS symptoms) and poor quality of life. Partners appear to have an important influence on SAHS patients' decisions about their health behaviour and further work should examine whether involving partners more closely in CPAP education can improve CPAP use.

## **CHAPTER 7 – CONCLUSIONS AND FUTURE WORK**

This thesis has explored aspects of CPAP treatment for SAHS. The factors influencing CPAP use have been investigated in detail, with particular attention to long-term use of CPAP. The effect of CPAP on the sleep quality of the patient and partner has also been investigated using a randomised placebo controlled study design.

Long-term CPAP use is an important measure of compliance with CPAP treatment because other treatment alternatives are often sub-optimal and many patients who are unable or unwilling to tolerate CPAP treatment in the long-term may not receive an effective alternative treatment. We followed-up a large cohort of patients who were booked for CPAP over an eleven year period. As there is very little long-term CPAP use data, particularly with objective measures of use, we believe the findings of this study add important clinical information about CPAP treatment. Unsurprisingly, long-term continuation of CPAP treatment was not perfect, with about one third of all those who started on CPAP stopping treatment by 5 years. However, it must be stressed that the Edinburgh cohort includes a large number of mild patients (17.5% with  $AHI < 15$  and 39.5% with  $ESS \leq 10$ ) because of our research interest in mild SAHS and this will bias the overall results. In those patients with an  $AHI \geq 15$  and  $ESS > 10$  at least 70% were still using CPAP at 5 years. Future work could continue the follow-up period in this cohort of patients, to see if CPAP use reaches a plateau or falls further with time.

The current long-term use data means that many patients in whom treatment for SAHS was clinically indicated will, with time, need to try alternative forms of



therapy or will be untreated. There is clearly a need to define the role of second-line therapies, such as MRS devices, for patients who are CPAP treatment failures. The compliance with such second-line therapies may also be sub-optimal in this setting. As an initial approach to this problem a descriptive study of acceptance, nightly, and long-term use of alternative therapies, when CPAP treatment has failed, would be of interest. One problem in this area is the difficulty in finding a simple and effective method of objectively monitoring the use of such devices. Ideally, all patients who do not continue CPAP long-term should be reassessed and offered alternative treatment. It would also be valuable to re-study CPAP failed patients overnight on second-line treatments to determine the effectiveness of such treatments in controlling SDB.

One of the main areas of interest in studies of CPAP use is in identifying pre-treatment predictors of use. We found that the important independent predictors of long-term CPAP use were the level of pre-treatment sleepiness and the severity of SDB. This is in keeping with some other studies but with the use of a large database we were able to establish the independent role of these variables. The small size of many previous studies and the weak predictive ability of pre-treatment variables probably explains why earlier work gave conflicting results. Unfortunately, the weak predictive role of these variables means that they are still, at best, a rough guide to who will and who will not be likely to continue treatment long-term. Nevertheless, combining the variables means that prediction can be improved. It is useful to know that most of those with an ESS  $\leq 10$  and AHI  $< 15$  are unlikely to continue long-term CPAP treatment. It is possible that this group may gain more

benefit from alternative therapies. There are currently studies in this and other units comparing CPAP with MRS for patients with mild disease ( $AHI < 15$ ) to determine the role of MRS in these patients.

In the absence of strong baseline predictors of long-term CPAP use many patients will merit a trial of CPAP treatment but will then not continue long-term. It would be useful to be able to identify early on those who have a low likelihood of continuing CPAP treatment. In this thesis, the nightly CPAP use within the first 3 months was found to be a strong predictor of long-term CPAP use. Early ( $< 3$  months) average nightly use of 2hr/night will separate most long-term users from the remainder with an odds ratio of 13.8. As the role for alternative therapies become better understood many patients with a low likelihood of continuing CPAP may be able to change early on to another form of therapy. Some of these patients may, however, benefit from increased support and education about CPAP during this early period when patterns of CPAP use (Kribbs et al. 1993b, Weaver et al. 1997a) and risk of long-term CPAP use (chapter 4) are established.

Previous work at this unit has established that a programme of intensive CPAP education and follow-up support can improve nightly CPAP use and treatment benefits (Hoy et al. 1999). Further work could focus such a programme on those who have low nightly CPAP use shortly after starting CPAP. This would involve downloading CPAP nightly use data from CPAP machines within the first month after starting CPAP. Those with low average nightly use could then be randomised to increased support or conventional follow-up (see chapter 3.2.3). Outcome measures would include CPAP nightly use at 6months and measures of benefit,

such as change in ESS, change in mood and cognitive function. Long-term CPAP use would be an important outcome measure but this would require larger patient numbers and longer term follow-up. If increased education and support are ineffective in this group it would suggest that a change in therapy should be tried instead for these patients.

Although, we also investigated the predictors of nightly CPAP use, the utility of this measure of CPAP compliance is less clear. Studies have suggested that missing a single night of CPAP treatment results in a return of sleepiness (Kribbs et al. 1993a), so that regularity of CPAP use seems to be important. Future studies should incorporate a measure of the regularity of nightly use. The minimum threshold of nightly use needed to obtain benefit is unknown. Further work on the equivalent of dose-response studies for medications, i.e., looking at the association of nightly CPAP use to benefit, would be useful. In one study, there was a dose-response effect of increasing nightly CPAP use on benefit in subjective and objective daytime sleepiness (Stradling & Davies 2000). Benefit does not seem to be the only factor in nightly use, however, as in the same study patients using sub-therapeutic CPAP, i.e., with no effective pressure, had nightly use (4.6hr) similar to those using therapeutic CPAP (5.4hr) (Jenkinson et al. 1999). Further, some patients (29%) are willing to continue long-term treatment (average follow-up, 10 months) for simple snoring with presumably little direct benefit to the patient (Rolfe et al. 1991). This underlies the importance of making measurements of benefit as well as CPAP use.

Acceptance of CPAP was better in our unit than reported elsewhere. This may be due to better patient selection. However, it also suggests that the education given in this unit (chapter 3.2.2) before starting treatment is important.

Analysis of data on CPAP use in this thesis was based on a database of patients booked for CPAP treatment between 1986-1997. There have been improvements in equipment (masks, headgear, and CPAP machines) over this time and there are new are likely to be further changes in equipment (e.g., intelligent CPAP) in the near future. This means that all of the findings reported here may not apply to patients receiving treatment with the current and new devices.

We used our database to determine if split-night studies were as effective as full night studies for long-term outcomes. As the predictors of long-term use were known, for this group of patients, these were appropriate matching variables. The split-night and matched full night groups were also well matched on other important variables (such as BMI). As little previous work had been done on outcomes in split-night studies these studies were performed relatively infrequently and our findings were based mainly on patients with classical symptoms of SAHS. For selected patients undergoing split-night studies there were similar long-term outcomes to full night patients, with similar follow-up care needed but less use of overnight hospital beds. The waiting time for treatment was also reduced. The number of patients booked for CPAP in our unit between 1986 and 1997 with an ESS>10 and AHI>30 was 249/1,211 (21%). Many of these will have classical symptoms of SAHS. This has important practical implications in view of the current high demand for sleep services. It would be useful to perform a prospective

controlled randomised study to confirm that these two methods of initiating CPAP have equivalent outcomes. Other ways of reducing demand for sleep services should be studied. Promising approaches include the use of in-laboratory or home diagnosis followed by automatic CPAP (see chapter 2.3.1), where titration pressure is determined on a continuous basis, as a means of saving the cost of hospital beds and reducing waiting times. Such approaches would need to be validated against the standard 2 full nights in the laboratory for diagnosis and treatment.

As the need for evidence-based decisions becomes increasingly important in medical practice it is necessary to establish the benefits of treatments using good randomised placebo controlled studies. Although there are now a number of randomised controlled studies showing that CPAP improves daytime function in SAHS, improvements in sleep quality had not been shown. We have established that CPAP improves objective measures of sleep quality in SAHS, using a randomised placebo controlled design. The lack of change found in REM sleep with CPAP is, perhaps, surprising but is in keeping with one controlled comparative study showing that only more severe SAHS patients show significant reductions in REM sleep, when compared with 'normal' subjects (Bedard et al. 1991). Hence, our failure to show a change in REM sleep might be because there is no such change or because the group of patients we studied had moderate severity disease.

We used the change in ESS (from placebo to 6-12 months on CPAP) as a measure of benefit from CPAP (chapter 6) and found that objective sleep quality on CPAP was associated with future benefit in ESS. By contrast, measures of objective sleep quality had little association with average nightly use (see above comments about



average nightly CPAP use). The strong associations between objective sleep quality on CPAP and later benefit in daytime sleepiness suggests that newer ways of giving CPAP (e.g., automatic CPAP machines), that lead to better sleep quality, may result in treatment benefits. Interestingly, the association between benefit from CPAP and objective sleep quality was stronger for sleep architecture variables such as SEI and stage 3+4 than for arousal index. This suggests that the effect of arousals on sleep architecture, and possibly on neuropeptides or other factors involved in sleep control (Chicurel 2000), may be more important than arousals per se.

The effect of SAHS on partners is an area that has received little attention despite the large number of people affected and the anecdotal evidence of widespread disturbance from SAHS symptoms. In this thesis we found that partners of patients with SAHS had poor sleep quality and poor quality of life, when compared to population normal values. CPAP treatment was beneficial to partners in improving their subjective sleep quality and perceived sleep disturbance but we were unable to demonstrate improvements in the partners' objective sleep quality. Partners reported that patients had improved sleep quality and daytime functioning with CPAP treatment and 18 of 22 partners preferred the patient to receive treatment with CPAP rather than a (placebo) capsule. Improvement in the partners' sleep quality was associated with CPAP use. This is compatible with the suggestion that partners may influence patients to use CPAP - or not to use it. If this is the case, education of partners may prove a simple means of improving CPAP compliance as was suggested by a previous study from our group (Hoy et al. 1999). Future work could survey partners for feedback on their concerns about SAHS and its treatment as well as what information and support they would like to have. However, it is

unclear from the current results whether partners influence patients to increase CPAP use or if there is better partner sleep quality when patients CPAP use is good. One way that to establish cause and effect is through an intervention study such as the use of education/support for partners. Couples could be randomised to a partner education/support group or a control group without specific education for partners. Outcomes assessed would include measures of CPAP compliance and benefit.

CPAP therapy was first used for the SAHS in 1981, when it was thought to be a treatment that could be used as a short-term measure until better treatments were developed. Two decades have passed and CPAP is still the preferred treatment for most patients with SAHS. This thesis has investigated some of the problems associated with CPAP use. Further work is needed to better understand which patients are most likely to use and benefit from CPAP, and which patients may be better off using alternative therapies. The ongoing challenge is to develop more patient-friendly, and partner-friendly, methods of delivering CPAP for those that need this treatment. At the same time research into alternative treatments to cure SAHS, either by the use of a drug therapy or surgical therapy, should be pursued.



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***Appendix a) – Sleep-wake questionnaires***

*(given to all individuals referred to the Edinburgh sleep centre with a suspected sleep disorder)*

NAME : .....

DATE : .....

Please find enclosed two questionnaires, one for you (marked patient) and a shorter one (marked partner) for your partner if you have one. The aim of these simple questionnaires is to discover the extent of your problem. It would be very helpful if you could arrange to fill them in and hand them to the doctor seeing you in the hospital clinic or to the Sleep Laboratory, Ward 48, Royal Infirmary of Edinburgh, at your next visit.

The questionnaire for your partner should be filled in independently by him/her without consulting you. You may get help, however, from your partner in answering Questions 9, 11 and 20.

For most questions several options are available, underline the answer which is most appropriate.

The answers will form part of your medical records and remain confidential.

Thank you for your co-operation.

PERSONAL INFORMATION: ..... DATE: .....

Name: ..... Age: ..... Date of Birth : .....

Address : .....  
.....  
.....

Tel No: .....

Marital Status: single/married/divorced/widowed.....

Collar Size : .....

		<u>Sex</u>	<u>Age</u>
Children:	Number : .....	....	....
		....	....
		....	....

Occupation:	current .....	for .....	years
	previous .....	for .....	years
	.....	for .....	years
	.....	for .....	years

Are you a : smoker / non-smoker / ex-smoker (for ..... years)

What did / do you smoke:	cigarettes	yes/no	Number per day .....
	cigars	yes/no	Number per day .....
	tobacco (own rolled)	yes/no	Oz. per week .....
	tobacco (pipe)	yes/no	Oz. per week .....

Do you drink:	tea	yes/no	cups per day .....
	coffee	yes/no	cups per day .....
	wine	yes/no	glasses per day .....
	beer	yes/no	pints per week .....
	spirits	yes/no	drinks per week .....
	sherry/port	yes/no	glasses per week. ....

Any alcohol immediately before going to bed: yes/no

What medication, including sleeping pills are you taking at present?

	<u>Name</u>	<u>Dose</u>	<u>How long have you been taking it?</u>
1.	.....	.....	.....
2.	.....	.....	.....
3.	.....	.....	.....
4.	.....	.....	.....
5.	.....	.....	.....

PAST MEDICAL HISTORY

If you have had the following illnesses, please give details:

<u>Illness</u>		
Asthma	yes/no	.....
Bronchitis	yes/no	.....
Emphysema	yes/no	.....
Diabetes	yes/no	.....
Heart attacks	yes/no	.....
High blood pressure	yes/no	.....
Ankle swelling	yes/no	.....
Tonsillitis	yes/no	.....
Hay fever	yes/no	.....
Broken nose	yes/no	.....
Bed wetting	yes/no	.....
Nerve problems	yes/no	.....
Nose operations	yes/no	.....
Throat operations	yes/no	.....

\*\*\*\*\*

1. When do you go to bed at night on average?
2. When do you finally wake up in the morning on average?
3. How long do you take to fall asleep at night?
4. How often do you wake between going to bed and getting up in the morning?  
never / 1-3 times / 3-6 times / more than 6 times per night
5. Do you do shift work? If so, please specify shifts and how long you are on each shift  
.....
6. How many times have you wet the bed in the last year?  
never / occasionally / 2-6 times / more than 6 times
7. How often have you woken with a headache each week?  
never / 1-2 times / 2-5 times / more than 5 times
8. How likely are you to doze off or fall asleep, in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0	=	would <b>never</b> doze
1	=	<b>slight</b> chance of dozing
2	=	<b>moderate</b> chance of dozing
3	=	<b>high</b> chance of dozing

<u>Situation</u>	<u>Chance of Dozing</u>
Sitting and reading	.....
Watching TV	.....
Sitting, inactive in a public place (eg a theatre or a meeting)	.....
As a passenger in a car for an hour without a break	.....
Lying down to rest in the afternoon when circumstances permit	.....
Sitting and talking to someone	.....
Sitting quietly after a lunch without alcohol	.....
In a car, while stopped for a few minutes in traffic	.....
<b>TOTAL</b>	<u>=====</u>

9. Do you snore during sleep?  
Yes/No  
If yes:
  - a) How long have you snored loudly?  
Always (since childhood / last 5 years / 3 years / 1 year
  - b) Do you snore every night / most nights/ occasional nights
  - c) Do you snore on your back only / on back and side / in all positions

10. Do you have a regular bed-partner or room-mate?  
yes / no / previously but not currently
11. Has your bed-partner/room-mate ever noticed that you stop breathing when asleep?  
yes / no
12. Do you need to go to the toilet at night?  
never / occasionally / 1-2 times / more than 2 times per night
13. Do your ankles swell? If so, for how long  
yes / no ..... months / years
14. Have you ever had hallucinations when you have been falling off to sleep or waking up?  
yes / no
15. Have you ever had episodes when your body or part of your body has become floppy in response to an emotional stimulus?  
yes / no
16. Have you ever had episodes when you have woken up and been unable to move?  
yes / no  
If so, how often?  
once / less than 5 times / more than 5 times
17. In the morning do you feel that your nights sleep was refreshing/satisfactory?  
always / 4-6 nights per week / 1-3 nights per week / never
18. Have you or your partner noticed any change in your sex drive?  
increased / unchanged / decreased / non-existent
19. How many times have you woken choking or suffocating in the past month?  
never / 1-2 times / 3-6 times / more than 6 times
20. How often is your bed-partner or room-mate, disturbed each week because of excessive arm and/or leg movements?  
never / 1-5 times / 5-10 times / more than 10 times / no bed partner
21. Are you ever forced to have a nap during the day?  
yes / no  
If so, how many naps (5 minutes) do you have per day?  
1-2 / 2-4 / 4-6 / more than 6
22. How many times have you fallen asleep against your will (for example, while eating, driving or in company) in the last year?  
never / 1-2 / 2-4 / more than 4 (give details below)
23. For how long have you been sleepy during the day?  
3 months / 3-6 months / 6-12 months / over 12 months / over 10 years
24. Do you drive?  
yes / no
25. Have you ever had, or nearly had an accident because of falling asleep while driving?  
yes / no (give details below)

26. Have you, your partner or family noticed any change in your personality?

yes / no

If so, specify :

.....  
.....  
.....

27. Has your weight changed in recent years?

yes / no

down / up

If so, what is the change

..... stones

..... lbs

When did your weight change occur :

.....

28. Have you any comments on the questions above?

.....  
.....  
.....  
.....

Additional comments:

.....  
.....  
.....  
.....  
.....

NAME : .....

DATE : .....

*Appendix a) – Sleep-wake questionnaire: partner*

PERSONAL INFORMATION:

DATE: .....

NAME: .....

AGE: .....

DATE OF BIRTH: .....

1. Does your partner drink?

tea	yes/no	cups per day	.....
coffee	yes/no	cups per day	.....
wine	yes/no	glasses per day	.....
beer	yes/no	pints per week	.....
spirits	yes/no	drinks per week	.....
sherry/port	yes/no	glasses per week	.....

Any alcohol immediately before going to bed:      yes/no

2. How likely does your partner doze off or fall asleep, in the following situations, in contrast to feeling just tired? This refers to his/her usual way of life in recent times. Even if they have not done some of these things recently, try to work out how they would have affected him/her. Use the following scale to choose the most appropriate number for each situation.

0	=	would <b>never</b> doze
1	=	<b>slight</b> chance of dozing
2	=	<b>moderate</b> chance of dozing
3	=	<b>high</b> chance of dozing

Situation

Chance of Dozing

Sitting and reading

.....

Watching TV

.....

Sitting, inactive in a public place (eg a theatre or a meeting)

.....

As a passenger in a car for an hour without a break

.....

Lying down to rest in the afternoon when circumstances permit

.....

Sitting and talking to someone

.....

Sitting quietly after a lunch without alcohol

.....

In a car, while stopped for a few minutes in traffic

.....

**TOTAL**

=====

3. Is your partner forced to have a nap during the day?

yes / no

If so, how many naps (5 minutes) does he/she have per day?



1-2 / 2-4 / 4-6 / more than 6

4. How many times has your partner fallen asleep against his/her will (for example, while eating, driving or in company) in the last year?

never / 1-2 / 2-4 / more than 4 (give details below)

5. For how long has your partner been sleepy during the day?

3 months / 3-6 months / 6-12 months / over 12 months / over 10 years

6. Does your partner drive?

yes / no

7. Has your partner ever had, or nearly had an accident because of falling asleep while driving?

yes / no (give details below)

8. Has your partner or family noticed any change in his/her personality?

yes / no

If so, specify:

.....

.....

.....

.....

**Appendix b –Baseline in-house questionnaire for sleep quality studies**

**THIS QUESTIONNAIRE IS FOR Partner's name ONLY.**

Please complete these questionnaires separately, ie without discussing with your partner.

Please tick or circle the most appropriate response

1. On a typical night, in the past month, how much is your sleep disturbed by your partner's?:

- a) snoring                      not at all / to a mild degree / to a moderate degree / severely disturbed
- b) breathing pauses              not at all / to a mild degree / to a moderate degree / severely disturbed
- c) restlessness                      not at all / to a mild degree / to a moderate degree / severely disturbed

2. How do you rate YOUR overall sleep quality on a typical night in the past month?

excellent / good / fair / very poor

3. Which person do you think decided that your partner's symptoms of sleep apnoea needed medical attention?

you did / your partner did / both of you equally

**THIS QUESTIONNAIRE IS FOR Patient's name ONLY.**

Please tick or circle the most appropriate response

Circle which was the main reason you had for seeking medical attention for this problem?  
(circle one only)

Disturbance caused by snoring  
Sleepiness/tiredness during the day  
Concern about breathing pauses during sleep  
Other = \_\_\_\_\_

Which person do you think decided that your symptoms of sleep apnoea needed medical attention?

you did / your partner did / both of you equally

*Appendix b – Crossover in-house questionnaire for sleep quality studies (at the end of each study limb)*

THIS QUESTIONNAIRE IS FOR \_\_\_\_\_ *Partner's name* \_\_\_\_\_ ONLY.

How many nights per week do you currently share a bed with your partner (out of 7)? \_\_\_\_\_

Please tick or circle the most appropriate response below

.....  
QUESTIONS ABOUT YOU:

1. How do you rate YOUR overall sleep quality on a typical night in the past month?

excellent / good / fair / very poor

2. On a typical night, in the past month, how much is your sleep disturbed by your partner's?:

- |                     |   |
|---------------------|---|
| a) snoring          | not at all / to a mild degree / to a moderate degree / severely disturbed |
| b) breathing pauses | not at all / to a mild degree / to a moderate degree / severely disturbed |
| c) restlessness     | not at all / to a mild degree / to a moderate degree / severely disturbed |
| d) CPAP machine     | not at all / to a mild degree / to a moderate degree / severely disturbed |

Compared to before your partner started treatment -

3. How much do you think the CPAP/capsule treatment has affected your sleep quality?

**no change**

**improved it:** to a mild degree / to a moderate degree / greatly

**worsened it:** to a mild degree / to a moderate degree / greatly

.....  
QUESTIONS ABOUT YOUR PARTNER:

Compared to before starting any treatment -

4. How much do you think CPAP/capsule has affected your partner's sleep quality?

**no change**

**improved it:** to a mild degree / to a moderate degree / greatly

**worsened it:** to a mild degree / to a moderate degree / greatly

5. How much do you think CPAP/capsule has affected your partner's daily functioning?

**no change**

**improved it:** to a mild degree / to a moderate degree / greatly

**worsened it:** to a mild degree / to a moderate degree / greatly

ON THE FINAL STUDY LIMB:

6. Overall, which of the treatments would you prefer your partner to use? CAPSULE/CPAP

## *Appendix c)*

### **Papers, abstracts, and presentations resulting from this thesis:**

#### **Papers:**

McArdle N, Devereux G, Heidarnajad H, Engleman HM, Mackay T, Douglas NJ. Long-term use of CPAP therapy for the sleep apnoea/hypopnoea syndrome, *Am J Resp Crit Care Med.* 1999; 159: 1108-1114.

McArdle N, Grove A, Devereux G, Mackay-Brown L, Mackay T, Douglas NJ. A matched controlled comparison of outcomes for split-night versus full night studies for sleep apnoea/hypopnoea syndrome, *Eur Respir J.* 2000; 15: 670-5.

#### **Abstracts and presentations:**

McArdle N, Devereux G, Heidarnajad H, Engleman HM, Mackay T, Douglas NJ. Determinants of discontinuation of CPAP therapy, *Am J Resp Crit Care Med.* 1998;3:A344.

McArdle N, Grove A, Devereux G, Mackay-Brown L, Mackay T, Douglas NJ. A matched controlled comparison of the efficacy of CPAP based on split-night studies compared with full polysomnography plus CPAP titration night. *Am J Resp Crit Care Med.* 1999; 159: A795.

McArdle N, Douglas NJ. Randomised crossover study of sleep quality of bed-partners of patients with sleep apnea/hypopnea syndrome. *Am J Resp Crit Care Med.* 2000; 161: Abstract, C89.

Patterns of CPAP use at the Scottish National Sleep Centre - British Thoracic Society winter meeting (London), 1997

The use of CPAP - Scottish Association for Sleep Apnoea (Edinburgh), 1998

Matched controlled comparison of CPAP based on split-night studies compared with Full polysomnography plus CPAP titration - British Sleep Society meeting (Liverpool), 1998

The role of split-night studies in the diagnosis of Sleep apnoea syndrome - Scottish Thoracic Society summer meeting (Creiff), 1999

The effect of sleep apnoea on partners of patients with sleep apnoea/hypopnoea syndrome - Scottish Association for Sleep Apnoea (Edinburgh), 2000

Randomised crossover study of sleep architecture on CPAP vs placebo in patients with sleep apnoea/hypopnoeas syndrome - Scottish Thoracic Society summer meeting (Creiff), 2000